Respiratory regulation and consequences of CO2 changes in panic disorder

RESPIRATORY REGULATION AND CONSEQUENCES OF CO_2 CHANGES IN PANIC DISORDER

ADEMHALINGSREGULATIE EN GEVOLGEN VAN CO_2 VERANDERINGEN BIJ PANIEKSTOORNIS

RESPIRATORY REGULATION AND CONSEQUENCES OF CO_2 CHANGES IN PANIC DISORDER

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen op
donderdag 23 januari 1992 om 16.00 uur

door

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Promotoren

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CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Zandbergen, Jan

Respiratory regulation and consequences of CO_2 changes in
panic disorder/ Jan Zandbergen; [ill. by the author]. -
[S.l. : s.n.] (Meppel : Krips Repro). - Ill.
Thesis Maastricht.- With ref. - With summary in Dutch.
ISBN 90-9004729-8
NUGI 744 / 745
Subject headings: panic disorder / respiratory regulation

Produktie en druk: Datawyse Maastricht/Krips Repro Meppel

CONTENTS

SUMMARY

This dissertation contains a series of studies on the occurence and pathogenetic role of respiratory disregulation in panic disorder.
Chapter 1 is an introduction on panic disorder, respiratory physiology, and their relationships. In 1.1 the panic disorder syndrome is briefly described. After a short sketch of the history, clinical picture and differential diagnosis, a summary of various theories on the etiology of panic is given. Chapter 1.2 contains a short overview of relevant aspects of respiratory physiology. Basic definitions and concepts concerning respiration, its control and acid-base balance are included. Furthermore, it introduces the concept of the ventilatory response to CO2 as a measure of respiratory control, and the methods to assess this CO2 sensitivity.
In Chapter 1.3 literature on respiratory aspects in panic disorder is reviewed, with an emphasis on remaining questions which led to the studies of the present dissertation.
Chapter 1.4 gives an overview of the studies for this thesis, their interrelations, and the reasons they were conducted.
Chapter 2 contains the reports on the empirical studies. Chapter 2.1 reports that panic disorder patients do not show clinically significant signs of hyperventilation in the absence of a panic attack.
Chapter 2.2 includes 3 studies on the anxiogenic role of experimental induction of pCO2 alterations in panic patients. In contrast to hypercarbia, hypocarbia appeared to induce hardly any anxiety. CO2 provoked anxiety proved to correlate best with respiratory symptoms.
In chapter 2.3 the possibility of respiratory disregulation in panic disorder is further explored. Breath-holding capacity appeared to be mainly determined by anxiety and/or the suffering of an anxiety disorder, although PD patients showed a small trend towards lower breath-holding times than other anxiety disorder patients. Ventilatory response to CO2 was found to be similar in panic disorder, obsessive-compulsive disorder, and healthy controls. In the pilot study on life time prevalence of respiratory diseases panic patients reported to have suffered from respiratory diseases in childhood more often than obsessive-compulsive disorder and eating disorder patients. These results should however be confirmed in additional studies.
Chapter 3 discusses the effects of hypercapnia and other disturbances in the acid-base balance from a neurophysiological perspective.
Finally, in chapter 4 the conclusions from the empirical studies are summarized. It also contains suggestions for future research.

SAMENVATTING

Dit proefschrift bevat een serie studies over het vóórkomen en de pathogenetische rol van stoornissen in de ademhalings-regulatie bij paniekstoornis.
Hoofdstuk 1 is een introductie over paniekstoornis, fysiologie van de ademhaling en de relaties daartussen. In 1.1 wordt het syndroom paniekstoornis kort beschreven. Na een schets van de geschiedenis, het klinisch beeld en de differentiaal diagnose volgt een samenvatting van diverse theorieën over de oorzaken van paniek. Hoofdstuk 1.2 bevat een kort overzicht van relevante aspecten van de ademhalings-fysiologie, waaronder basale definities en begrippen betreffende ademhaling, de controle daarvan en het zuur-base evenwicht. Bovendien wordt de ventilatoire respons op CO2 als een maat voor ademhalingscontrole geïntroduceerd, alsmede de methoden om deze CO2 gevoeligheid te bepalen.
In hoofdstuk 1.3 wordt de literatuur over ademhalingsaspecten bij paniekstoornis bediscussieerd, waarbij de nadruk ligt op de vraagstellingen die geleid hebben tot de studies in dit proefschrift.
Hoofdstuk 1.4 geeft een overzicht van de empirische studies, de onderlinge samenhang en de redenen waarom ze werden uitgevoerd.
Hoofdstuk 2 bevat de verslagen van de diverse studies. In 2.1 wordt gerapporteerd dat patiënten met paniekstoornis geen klinisch significante tekenen van hyperventilatie vertoonden buiten hun paniekaanvallen.
Hoofdstuk 2.2 bevat 3 studies over de invloed van experimentele veranderingen van de CO2-spanning op het angstniveau bij paniekpatiënten. In tegenstelling tot hypercarbie bleek hypocarbie nauwelijks enige angst op te roepen. Tevens werd gevonden dat CO2 geïnduceerde angst met name correleerde met ademhalingssymptomen.
In de studies in hoofdstuk 2.3 werd de mogelijkheid van stoornissen van de ademhalingsregulatie bij paniekstoornis verder onderzocht. Het vermogen om de adem in te houden bleek voornamelijk te worden bepaald door de mate van angst en/of het lijden aan een angststoornis, hoewel er een kleine trend was naar kortere ademhalingstijden bij paniekpatiënten dan bij patiënten met een andere angststoornis. De ventilatoire respons op CO2 was gelijkwaardig in paniekstoornis, obsessieve-compulsieve stoornis en gezonde controle personen. In de pilot-studie over de prevalentie van ziekten van ademhalingsorganen werd gevonden, dat paniekpatiënten vaker rapporteerden, dat ze tijdens hun kinderjaren geleden hadden aan ademhalingsziekten, dan obsessieve-compulsieve stoornis- en eetstoornispatiënten. Deze resultaten moeten echter in aanvullende studies bevestigd worden.
Hoofdstuk 3 bediscussieerd de effecten van hypercapnie en andere verstoringen in het zuur-base evenwicht vanuit een neurofysiologisch gezichtspunt.
Tenslotte worden in hoofdstuk 4 de conclusies van de empirische studies samengevat. Het bevat tevens suggesties voor verder onderzoek.

CHAPTER 1: INTRODUCTION

1.1 PANIC DISORDER

1.1.1 History

During the last century, a great variety of diagnostic names have been used to describe syndromes, which highly resemble or represent the same clinical picture as what is now being referred to as panic disorder. One of the earliest descriptions came from DaCosta (1871), who reported on Civil War soldiers suffering from an "irritable heart" or "DaCosta's syndrome". A few of the other names which have been used to describe syndromes with similar symptoms are "effort syndrome" (Lewis, 1919) and "neurocirculatory asthenia" (Oppenheimer et al., 1918).
Probably, the most influential description over the past century has been that of "anxiety neurosis" (Freud, 1894). This syndrome included both patients with discrete panic episodes and patients with chronic anxiety.
It was not until 1980 with the publication of the DSM-III (APA, 1980) that "anxiety neurosis" was divided into 2 separate diagnostic categories (panic disorder (PD) and generalized anxiety disorder (GAD)). The reasons for the division as such was due to observations of differing natural course and response to drug treatment. PD, which is characterized by discrete periods of intense fear, was found to be responsive to (some) tricyclic antidepressants, whereas GAD patients, who experience chronic anxiety, were less responsive to these drugs, but more so to benzodiazepines (Klein, 1964). Although later studies found that PD patients could improve on some specific benzodiazepines such as alprazolam (Klerman, 1988; Ballenger et al., 1988) and clonazepam (Spier et al., 1986; Tesar et al., 1987; Pols et al., 1991), and that GAD patients might also be responsive to tricyclic antidepressants (Kahn et al., 1987), the distinction between PD and GAD was considered valid enough to be retained in the revised version of the DSM-III (DSM- III-R, APA, 1987).
As already observed by Freud, many patients suffer from both panic attacks and agoraphobia, the fear of being in public places. In the DSM-III-R this regularly occuring association is reflected by the definition of 2 types of PD: PD with agoraphobia (DSM-III-R 300.21) and PD without agoraphobia (DSM- III-R 300.01).

1.1.2 Clinical description

EPIDEMIOLOGY

Estimations concerning lifetime prevalence of panic disorder in the general population vary from 1 to 5 percent (Robins et al., 1984; Kaplan & Sadock, 1988), although up to 35 percent of the general population may have experienced at least one panic attack during their life time (Von Korff, 1985). The incidence of panic disorder without agoraphobia seems to be equal in women and men, while the female-to-male ratio is

approximately 2 to 1 for panic disorder with agoraphobia (DSM-III-R, 1987; Kaplan & Sadock, 1988). Usually, onset of panic disorder is in young adulthood, although it may develop in younger and older subjects.

CLINICAL SIGNS AND SYMPTOMS
(DSM-III-R, APA, 1987; Kaplan & Sadock, 1988; Griez, 1990)

The essential features of panic disorder are recurrent and unexpected panic attacks. Panic attacks are characterized by an abrupt onset (within 10 minutes) of fear, apprehension or discomfort, accompanied by at least 4 symptoms such as dyspnea or smothering sensations, choking, chest pain, palpitations, and dizziness (table 1).

Table 1: Panic attack (DSM-III-R, APA, 1987)

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* discrete period with unexpected and abrupt onset of intense fear or discomfort

* within several minutes development of at least 4 of the following symtpoms:
  - dyspnea
  - dizziness or faintness
  - palpitations or tachycardia
  - trembling
  - sweating
  - choking
  - nausea or abdominal distress
  - depersonalization/derealization
  - paresthesias
  - flushes or chills
  - chest pain/discomfort
  - fear of dying
  - fear of going crazy/doing something uncontrolled

When less than 4 symptoms occur, attacks are referred to as limited or minor panic attacks. During a panic attack the patients may believe that he/she is suffering from a severe somatic condition, for instance a heart attack, and seek acute medical help. Typically, panic attacks last several minutes, and rarely, more than an hour, with symptoms generally disappearing gradually. The onset of panic attacks is, at least initially, unexpected and unpredictable, although in the course of the disorder panic attacks may also be provoked by various places or situations.
Panic disorder (PD) patients often have 1 or 2 panic attacks per week; sometimes there are several a day. The severity and frequency of panic attacks may fluctuate.
The nature of symptoms during panic attacks shows considerable interindividual variability. Lelliot & Bass (1990) distinguish 4 symptom clusters (respiratory, cardio-

vascular, neurological, and gastro-intestinal), which may occur to varying degrees and proportions between PD patients.

ASSOCIATED PHENOMENA

Many PD patients suffer from anticipatory anxiety (concern about future panic attacks) and generalized anxiety symptoms in between their attacks. Generalized anxiety symptoms can begin after various panic attacks have occured, but can also precede the onset of panic attacks (Breier et al., 1986; Garvey et al., 1988; Fava et al., 1988).
Panic disorder is frequently associated with agoraphobia. The causal link between these is however unclear. Biologically oriented investigators have viewed agoraphobic avoidance as a consequence of panic attacks (Klein, 1987). In contrast, behaviorists have considered agoraphobia as the primary disorder, with panic attacks as a secondary phenomenum (Marks, 1987). Research data have shown that agoraphobia can precede (Fava et al., 1988) as well as follow (Uhde et al., 1985; Breier et al., 1986) the onset of panic attacks.
Other frequently co-occuring phenomena in PD include

- hypochondrical fears and beliefs (Fava et al., 1988)
- depression, which may occur in up to 70 percent of PD patients (Cloninger et al., 1981; Uhde et al., 1985; Breier et al., 1985, 1986)
- suicidal ideation and suicide attempts (Weissman et al., 1989)
- benzodiazepine and alcohol abuse (Woodruff et al., 1972; Breier et al., 1986)

1.1.3 Differential diagnosis

The psychiatric differential diagnosis includes depression, hypochondriasis, schizophrenia and various other anxiety disorders, including generalized anxiety disorder, social phobia and simple phobia (Kaplan & Sadock, 1988).
The organic differential diagnosis for panic is summarized in table 2.
Some of these somatic disorders seem of particular interest, since there are indications that they often co-occur with PD. Obviously, before the additional diagnosis of PD is made, it should be established that these somatic diseases are not directly responsible for initiating and maintaining the panic-like symptoms (DSM-III-R, APA, 1987).
One of the physical diseases which is frequently diagnosed in PD patients is mitral valve prolapse (Liberthson et al., 1986). The significance of this association is however unclear, and not without controversy. The frequency of vestibular disturbances might also be increased in PD (Jacob et al., 1985). The findings of higher prevalence of PD in subjects with chronic obstructive pulmonary disease than in the general population (Yellowlees et al., 1987; Karajgi et al., 1990) will be discussed in Chapter 1.3.4.

Table 2. Organic differential diagnosis for panic disorder.
(Kaplan & Sadock, 1988; Griez, 1990)

Cardiovascular	- Coronary artery occlusion - Paradoxical atrial tachycardia - Mitral valve prolapse
Respiratory	- Chronic obstructive pulmonary disease (asthma and bronchitis)
Neurological	- Epilepsy - Migraine - Vestibular disorders
Endocrine	- Thyroid dysregulation - Blood glucose dysregulation - Adrenal dysregulation - Carcinoid syndrome - Pheochromocytoma
Drug intoxications	- Amphetamine - Cocaine - Anticholinergics - Theophylline
Drug withdrawal	- Alcohol - Benzodiazepines

1.1.4 Etiology

The precise etiology of PD remains for the most part unknown. Given the heterogeneity of the syndrome (Lelliot & Bass, 1990) and the many factors influencing the occurence and the course of the syndrome, it seems unlikely that PD can be attributed to one single underlying pathogenetic distortion. The large variety of theories concerning the pathogenenesis of PD should then best be regarded as complementary to one another, each theory dealing with only one aspect of the total syndrome. It goes beyond the purpose of the present thesis to discuss all hypotheses in detail. Therefore, this chapter will be limited to merely giving a selective overview of the various lines of research and theories. Relevant topics will be discussed later.
A good number of theories concerning the etiology of PD are based on the following types of studies:

1. Measurements on PD patients "at rest", including
   - physiological parameters
   - substances in blood or cerebro-spinal fluid
   - psychological variables
   - social factors
2. Provocation studies:
   - challenges which directly influence the acid-base balance
   - various pharmacological agents
   - cognitive provocation tests
3. Neuroendocrine investigations
4. Treatment studies
5. Genetic studies
6. Brain imaging studies,
   such as positron emission tomography (PET)
7. Epidemiological studies,
   i.e. occurence of concommitant or previous diseases
8. Animal experiments

The results of these studies, although not always being equally interpreted, have given considerable information about the pathogenesis of panic.
There is increasing evidence in favor of a genetic predisposition to developing PD, as has been shown by family studies, twin studies and linkage studies (Crowe et al., 1983, 1987; Torgerson, 1983; Kendler, 1986). There may also be a genetic link with depression (Leckman et al., 1983; Kendler et al., 1987). It is not yet clear, however, which anatomical and/or pharmacological structures are precisely affected in this genetic predisposition and how this can lead to panic attacks.
One of the structures hypothesized as being involved in panic has been the locus ceruleus, located in the brainstem (Gorman et al., 1984b; Charney et al., 1984). It contains noradrenergic cell-bodies with projections to all parts of the brain. The locus ceruleus theory is however not without important controversy (for details see Gorman et al., 1989a). One of the arguments in favor of this hypothesis is the panicogenic effect in PD patients of Yohimbine, an alpha-2-receptor antagonist, which stimulates the locus ceruleus. It has been shown, that Yohimbine can provoke panic in PD patients (Charney et al., 1984), while healthy controls usually fail even to distinguish between yohimbine and placebo (Van den Hout, 1988). Furthermore, Clonidine, an alpha-2-receptor agonist, which decreases locus ceruleus activity, has been found to reduce panic attacks, although the effect was transient (Hoehn-Saric et al., 1981; Liebowitz et al., 1981). Finally, various cyclic antidepressants which influence the noradrenergic system, have been reported to be effective in panic (Lydiard & Ballenger, 1987; Cassano et al., 1988a).
On the other hand, various cyclic antidepressants which act almost exclusively by inhibiting serotonin re-uptake, are also effective in reducing panic attacks (Evans et al., 1986; Den Boer et al., 1987; Cassano et al., 1988b). Most serotonergic neurons derive from cell bodies in the raphe dorsalis region in the brainstem. The suggestion of involvement of these serotonergic pathways, is supported by findings of altered serotonin metabolism and increased sensitivity to serotonergic compounds in PD (Lingjaerde, 1985; Pols & Griez, 1988; Kahn et al., 1988).

Yet other investigators have put forward psychological explanations for natural and experimental panic. According to these cognitive theories various physical symptoms such as dyspnea and palpitations act as danger signals in PD patients (Salkovskis, 1987), and would lead to anxiety according to the principle of "catastrophic misinterpretation" (Clark, 1986) or "fear of symptoms" (Van den Hout et al., 1987). Many provocation methods, such as lactate, CO2 and hyperventilation have in common that they induce these frightening physical symptoms in PD subjects (Margraf et al., 1986). This cognitive explanation for panic is supported by the findings that the nature of instructions (reassuring or frightening), which subjects receive before undergoing a provocation test, has a clear influence on the anxiety they report during voluntary hyperventilation (in PD patients)(Margraf & Ehlers, 1987), CO2 inhalation (in PD patients)(Rapee et al., 1986), and lactate-infusions (in normals)(Van der Molen, et al., 1986). In an experiment reported by Ehlers et al. (1986), it was found that PD patients, receiving auditive feedback on their heart rate, responded with more anxiety than normals when the "true" feedback was replaced by an increased "false" feedback on heart rate. A final argument in favor of the cognitive model is the effectiveness of cognitive treatment in PD (Salkovskis & Clark, 1986).
These findings are quite convincingly supporting a role for cognitive mechanisms in panic. However, the model is silent about the nature and physiological basis of the sensations that are held to be catastrophically interpreted. Furthermore, it can not satisfactory explain the occurence of nocturnal panic attacks (Ley, 1988; Herman, 1988; Mellman & Uhde, 1989), the effectiveness of medication in PD, and the above mentioned findings that Yohimbine can provoke panic in PD patients (Charney et al., 1984), while normals are unable to distinguish between Yohimbine and placebo (Van den Hout, 1988). Studies on "real-life panic" have suggested that both cognitions and physiology may be important factors (Kenardy et al., 1988, 1989).
Psychoanalytic theories regard panic attacks as a result of unsuccesful defense against anxiety inducing impulses, while agoraphobia might be related to separation anxiety in childhood. However, recent research has shown that, although separation anxiety occured more frequently in PD patients than in normals, the incidence is approximately equal in PD, major depression and other neurotic disorders (Yeragani, et al., 1989; Van der Molen et al., 1989). Other reports suggest that PD patients experience more adversive life-events in the last year preceding the onset of their attacks than normal controls (Faravelli et al., 1985; Roy-Byrne, 1986), although this also holds for numerous other psychiatric and somatic diseases (Holmes & Rahe, 1967; Paykel & Hollyman, 1984). It does seem though that the number of life-events for the total life course up until the onset of the disorder is higher in PD than in obsessive- compulsive disorder (De Loof et al., 1989).
It could be argued that learning mechanisms contribute to developing anxiety, for instance by means of parental modeling or classical conditioning. Behavioral treatment has been demonstrated to be very succesful in PD, especially when it is complicated by agoraphobia (Marks, 1987).
Many of the above mentioned theories have been integrated in a model of PD proposed by Gorman et al. (1989a). They argue that acute panic attacks originate in the brainstem with stimulation of irritable loci in the noradrenergic locus ceruleus, the serotonergic dorsal raphe, and/or medullary chemoreceptors. Anticipatory anxiety, the second component of panic, would be located in the limbic system. The prefrontal cortex is

probably involved in more complex phenomena of PD. Here, panic attacks are labeled as dangerous and life-threatening events, while associations are made with environmental situations, thus possibly leading to agoraphobic avoidance.
A very influential hypothetic line, which has been the topic of interest of both biological and psychological approaches, is the possibility of respiratory dysregulation and acid-base disturbances in PD. It includes theories on hyperventilation, CO2 and lactate challenges, and CO2 chemoreceptivity. These matters, being the subject of the present thesis, will be discussed in more detail in the next chapters. Before doing so, it seems however useful to briefly review relevant definitions, concepts and findings from respiratory physiology.

1.2 SHORT OVERVIEW OF RESPIRATORY PHYSIOLOGY

1.2.1 Ventilation

In this chapter basic definitions and fundamental ideas concerning ventilation are summarized (Schmidt & Thews, 1980).
Figure 1 shows the various lung volumes and capacities.

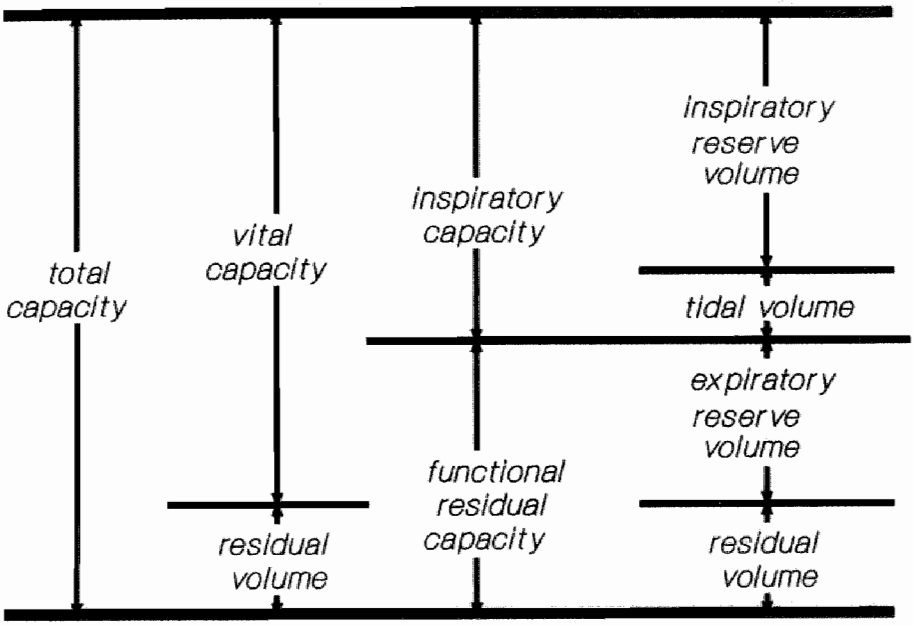

Figure 1. Lung volumes and capacities

The vital capacity, the difference in volume between maximal expiration and maximal inspiration, is influenced by various factors, including age, sex, body size, body

position, and the state of physical training. A measure not defined in fig.1 is FEV1, which is the amount of air which can be exhaled in 1 second during forced expiration. Usually the FEV1 is expressed as the ratio of the tidal volume. Until the age of 50 years normal values for FEV1 are 70-80% of the tidal volume.
Ventilation depends on the tidal volume, the difference in volume between expiration and inspiration, and the respiratory frequency. In healthy adults at rest the tidal volume is approximately 0.5 liter, while the respiratory frequency varies in normal circumstances between 10 and 18 breaths per minute. The respiratory minute volume, which is defined as tidal volume multiplied by respiratory frequency, is at rest usually approximately 6 to 7 liters per minute.
Gas exchange takes place in the alveoli. The "dead space" refers to the volume of the airways, where no gas interchange occurs. It includes the trachea, the bronchi and the bronchioli, and has a total volume of approximately 150 ml. One of the consequences of this "dead space" is that an increase in respiratory frequency has relatively less influence on alveolar ventilation than an increase in tidal volume.
The function of ventilation is to supply the blood with oxygen (O2) while removing carbondioxide (CO2). Inspiration air contains approximately 20 vol.% O2 and 0.03 vol.% CO2, which, at average atmospheric and water vapour pressure, correspond with partial pressure values of 150 mmHg (= 20 kPa) O2 and 0,2 mmHg (= 0.027 kPa) CO2. The partial pressure values in the end tidal expiration gas mixture, which during sufficiently deep respiration usually correspond with those in the alveoli, are normally 100 mmHg (13,3 kPa) for O2 and 40 mmHg (5,3 kPa) for CO2.
The arterial blood gas pressures depend on 4 factors:

1. alveolar ventilation
2. perfusion (pulmonary blood circulation)
3. diffusion (of O2 and CO2 from and to alveoli and pulmonary bloodvessels)
4. distribution of ventilation, perfusion, and diffusion over various parts of the lungs.

In healthy subjects, the arterial pO2 value is usually slightly lower than the alveolar partial pressure, while the arterial pCO2 value is approximateley equal or slightly higher than those in the alveoli. In pathological cirumstances arterial bloodgas values may however considerably differ from those in the alveoli.
Hyperventilation can be defined as a ventilation which exceeds metabolic needs. This discrepancy is reflected in decreased arterial pCO2. Although during hyperventilation arterial pO2 is increased, it hardly influences the amount of blood oxygen, as most haemoglobin is already almost completely saturated with O2 at a pO2 of 100 mmHg (= 13,3 kPa). Due to the lower pCO2 concentration, haemoglobin binds O2 more tightly (Bohr-effect), which may result in an even less efficient delivery of O2 to the tissues. A second consequence of the low pCO2 concentration is vascular constriction. It has been shown that during hyperventilation cerebral blood flow is markedly decreased (Guyton, 1976; Hauge et al., 1980). Hyperventilation can occur through increases in tidal volume and/or respiratory frequency.

1.2.2 Regulation of respiration

The main function of respiratory control is to maintain arterial pO2, pCO2 and pH constant. Information regarding values of these parameters are passed through to the central respiratory control center, which consists of various structures in the brainstem. This center then gives an output signal to the effector organs, the respiratory muscles, which determine alveolar ventilation, thus affecting arterial bloodgas values. In addition to this basic feedback mechanism many other factors may give input signals to the central respiratory control center or elsewhise influence respiration and ventilation. Figure 2 gives a simplified representation of the most relevant factors and their interactions. Some of these will be described in more detail.

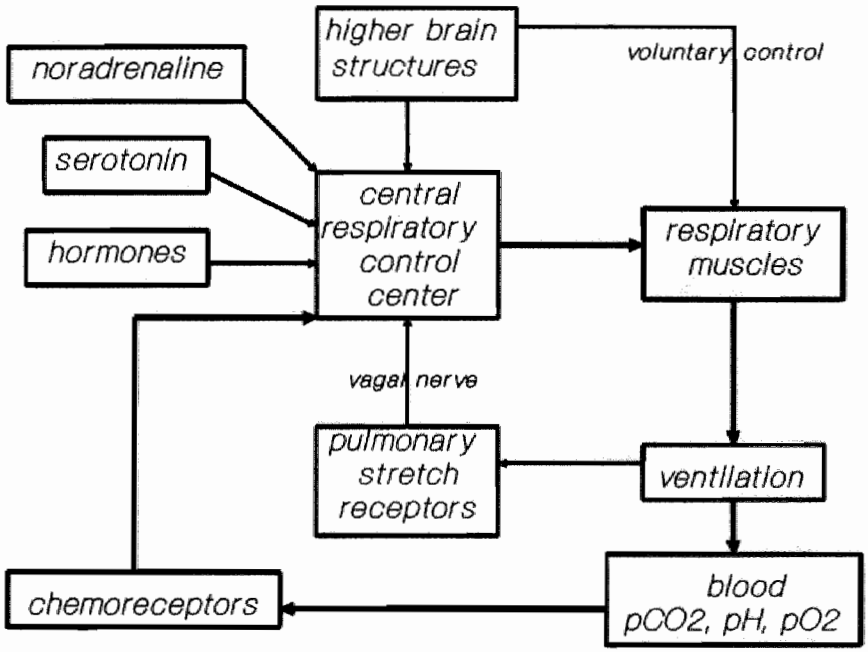

Figure 2. Regulation of respiration

RESPIRATORY MUSCLES (Schmidt & Thews, 1980)

During quiet respiration 2 types of breathing patterns are distinguished. In the abdominal breathing type the main muscular structure involved in inspiration is the diaphragma, innervated by the phrenic nerve. During the second breathing pattern, thoracic breathing, inspiration is effected by the external costal muscles and the intercartilagineal parts of the internal intercostal muscles. Thoracic breathing is less efficient than abdominal breathing and requires considerable muscular effort (Roussos & Engel, 1980). The accessory respiratory muscles, such as the scalenal and sternocleidomastoideal muscles, are used only during excessive respiratory demands.
Expiration is at rest mainly a passive process. Stronger expiration requires the activity of the interosseal parts of the internal intercostal muscles. The abdominal muscles may also be involved during expiration for excessive respiratory needs.
The respiratory muscles are influenced by the respiratory control center in the brainstem, but can also be affected by the motor cortex.

CHEMICAL CONTROL

In normal circumstances respiration is mainly determined by (changes in) arterial pCO2 (Schmidt & Thews, 1980). Respiratory responses appear to depend on the mean level of arterial pCO2, as well as by the rate of increase of arterial pCO2 (Dutton et al., 1964). Decreases in pH and pO2 may synergistically reinforce respiratory stimulation due to pCO2 increase (Schmidt & Thews, 1980; Teppema et al., 1983).
The central chemoreceptors, located in the ventral surface of the medulla, are stimulated only by CO2 and H+ (for details see chapter 3). The peripheral chemoreceptors are located in the carotid body at the bifurcation of the carotid arteries, and in the aortic bodies. They give impulses to the central respiratory center through the glossopharyngeal and vagal nerve respectively (Schmidt & Thews, 1980). The contribution of these peripheral chemoreceptors to respiration is usually small. They are mainly stimulated by decreases in pO2, but can also be influenced by alterations in the pCO2 and pH (Schmidt & Thews, 1980; Lahiri et al., 1981; Bowes et al., 1982). Hypotension may stimulate the peripheral chemoreceptors as well (Lahiri et al., 1980).

MECHANICAL CONTROL

Input from mechanical receptors influences tidal volume and timing of inspiration and expiration. Pulmonary stretch receptors located in the walls of small airways respond to lung volume increases. Via the afferent vagal nerve they inform the central ventilatory control center, thus inhibiting further inspiration. This mechanism is referred to as the Hering-Breuer-reflex (Schmidt & Thews, 1980). Inhalation of chemical and mechanical irritants, and pulmonary diseases as asthma may lead to hyperpnea through stimulation of other lung receptors, which are referred to as "irritant receptors" and "J-receptors" (Berger et al., 1977).
It has been argued that dyspnea, the feeling of being breathless, partially depends on proprioceptive information from the chest wall (i.e intercostal muscle spindles). This

information would be influenced by muscular effort of overcoming respiratory resistance and the position of the chest wall (Cohn, 1983; Jones et al., 1990).

CENTRAL RESPIRATORY CONTROL (Mueller et al., 1982)

The central respiratory control center includes various clusters of cells in the medulla and pons with mutual interactions. They receive input from the above mentioned chemoreceptors and mechanical receptors, and project to motor neurons in the spinal cord, which innervate the diagphragma and intercostal muscles. The structures in the medulla probably represent the primary respiratory rhythm generator, while nuclei in the pons play a modulating role.
Within the medullary center there are neurons which fire during specific phases of the respiratory cycle: some are active throughout the entire inspiration cycle: others only during early, late, or post inspiration, and some during expiration.
The ventral respiratory neurons in the medulla are associated with the nucleus retro ambiguus; they may fire during inspiration, expiration, or both. The nucleus ambiguus cells of the ventral respiratory neurons are probably mostly related to the accessory respiratory muscles. The dorsal respiratory neurons are associated with the nucleus tractus solitarius, and are inspiratory cells.
One of the structures in the pons which is involved in respiration is the nucleus parabrachialis medialis. It probably has a modulating influence on the medullary respiration control center. Terms which have also been used for centers in the pons include "apneustic center" and the "pneumotaxic center".

FURTHER INFLUENCES ON RESPIRATION

A great deal of research has indicated that noradrenergic and serotonergic activity may effect respiration. There is however no general agreement about the direction and exact mechanisms of these influences (Eldridge & Millhorn, 1981; Mueller et al., 1982). Concerning GABA (gamma-aminobutyric acid) activity, results more equivocally point to an inhibitory effect (Eldridge & Millhorn, 1981; Mueller et al., 1982). Benzodiazepines, which enhance GABA-mediated synaptic inhibition of central neurons, have been found to depress respiration (Dalen et al., 1969; Cohn, 1983).
Respiration may be influenced by various hormones. Progesterone, for instance, can stimulate respiration, as is reflected in slightly decreased alveolar pCO_2 in the luteal phase of the menstrual cycle; usually this drop in pCO_2 is less than 5 mmHg (England & Farhi, 1976; Takano et al., 1981).
Muscle activity, such as during physical exercise, requires greater ventilation because of greater metabolic demands. Chemical feedback mechanisms play an important role in this process. However, it is likely that, especially in the starting phase of physical exercise, the respiratory center also receives impulses from higher brain centers (Schmidt & Thews, 1980).
There are more indications that higher brain structures influence the respiratory control center (for an overview see Garssen (1986)). Psychological stress, for instance, can induce increases in respiratory rate, minute volume, changes in tidal volume, and as a

consequence, decreases in alveolar and blood CO2 levels as compared to baseline conditions (Grossman, 1983). Anticipation of an electrical shock during a perceptual task has been shown to induce increases in respiratory rate and decreases in end-tidal pCO2 (together with a rise in heart rate and anxiety scores (Suess et al., 1980). Van den Hout et al. (1991) showed that both watching an exciting film and fearful imagination lead to increases in distress, respiratory rate and variability of end-tidal CO2, and to decreases in mean end-tidal pCO2. Changes in pCO2 as a consequence of psychological stress are usually smaller than 5 mmHg.

1.2.3 Ventilatory response to CO_2

In the previous sections respiratory frequency, tidal volume, minute volume and arterial or end-tidal pCO2 have been outlined as parameters for respiratory control. Another measure of respiratory control can be obtained by assessment of the ventilatory response to CO2, also called the CO2 sensitivity. In this procedure ventilation is measured at different values of arterial pCO2, which is achieved by inhaling gasmixtures with various CO2 concentrations. Usually ventilation rises in a linear fashion with changes in arterial CO2 (Read, 1967). When pCO2 is plotted at the X- axis and respiratory minute volume at the Y-axis, the slope of the resulting regression line is taken as a measure for the CO2 sensitivity (RCO2). As hypoxia may effect RCO2, the test is usually performed in hyperoxic circumstances. The ventilatory response to CO2 is mainly determined by the pCO2 at the medullary chemoreceptors, while the carotid and aortic bodies have little influence on CO2 sensitivity (Wiemer et al., 1965). Therefore, RCO2 is often used as a measure of the sensitivity of central CO2 chemoreceptors, although ventilatory response to CO2 also depends on many other factors (see following sections).

METHODS FOR RCO2 ASSESSMENT

Basically, there are 2 different procedures for determining RCO2: the steady state method and the rebreathing method. In the steady state procedure subjects inhale gasmixtures with concentrations of CO2 of, for instance, 3, 5 and 7% , over a prolonged period of 10 to 20 minutes, while end-tidal or arterial blood pCO2 are measured (Read, 1967). In the steady-state procedure as described by Gorman et al. (1988) and Papp et al. (1989a), the subject's head is placed in a clear plastic canopy, which is vented with air and a gasmixture with 5% CO2. The canopy is connected to a spirometer, thus permitting measurement of minute volume. Arterial pCO2 values are derived from blood which is obtained via arterial lines.
In contrast to the steady-state procedure, the rebreathing method is fairly well standardized. In the latter procedure, as described by Read (1967), subjects rebreathe from a bag (or a spirometer), filled with 4 to 6 liter of an initial gas mixture of 7% CO2 and 93% O2 (or 7% CO2, 50% O2 and 43% N2). The pCO2 in the bag/spirometer is then slightly higher than the arterial pCO2. Within 40 seconds the pCO2 in the bag/spirometer, the alveoli, the arterial and the mixed venous blood equilibrate (Clark & Read, 1966). Usually rebreathing lasts 3 to 5 minutes, while pCO2 is gradually increasing with 3 to 6 mmHg per minute.

It has been demonstrated that values of RCO2 obtained by the 2 methods reasonably correspond (Read, 1967). However, with the steady-state method, the ventilation appeared to be greater at comparable leves of pCO2 (Read, 1967). In other words, the regression line found with the steady-state method is higher but parallel to the one found with the rebreathing method. This also means that the estimation of the extrapolated pCO2 intercept, indicating the hypothetical pCO2 providing zero stimulus to ventilation, will be higher when the rebreathing method is used.
The rebreathing method has the advantage that it is simple, rapid and more standardized than the steady-state method. The steady-state method as described by Gorman et al.(1988) and Papp et al. (1989a) may have the advantage that arterial blood gives more accurate measurements of pCO2. One of the arguments of Gorman et al. (1988) and Papp et al. (1989a) for using the steady-state canopy procedure is also that the canopy does not induce anxiety, at least in normals (Kinney, 1980), in contrast with the mouthpiece-noseclip arrangement which is used in the rebreathing procedure (Askanazi et al., 1980). However, this argument may not relate to PD patients, as many of them tend to be claustrophobic. Disadvantages of the procedure as used by Gorman et al. (1988) and Papp et al. (1989a) are that placing arterial lines is difficult to perform, while it carries a small risk of thrombus formation. In addition, it may be painful and induce anxiety.

DETERMINANTS OF CO2 SENSITIVITY

Measurement of RCO2 is quite reproducible over time within an individual in comparable circumstances (Read, 1967). There may however be great interindividual differences, normal values ranging from 0.5 to 9.0 liters/min/mmHg with an average value of approximately 2.5 (sd.1.0) liter/min/mmHg (Hirschman et al., 1975; Irsigler et al., 1976).
Many factors may influence RCO2. One of these is sex, women having slightly lower RCO2 values than men (Irsigler. 1976; Damas-Mora et al., 1978). Studies on the effect of age are inconsistent, some finding no influence (Irsigler, 1976), other finding a negative correlation between RCO2 and age (Damas-Mora et al., 1978). Body surface (Damas-Mora et al., 1978) and vital capacity (Irsigler, 1976) may also affect RCO2. During sleep RCO2 seems to be lower than in awakening subjects (Gothe et al., 1981). Personality traits such as extraversion and agression seem to correlate positively with RCO2, while social introversion correlates negatively with RCO2 (Saunders et al., 1972; Shersow et al., 1973; Arkinstall et al., 1974), although others (Singh, 1984) could not replicate these findings. RCO2 has been shown to be decreased in depression (Shersow et al., 1976; Damas-Mora et al., 1978).Various drugs may also influence RCO2 (Lambertsen, 1964; Cohn, 1983). Benzodiazepines, for instance, have been reported to decrease RCO2, although a few studies found an increased RCO2 (for an overview see Cohn, 1983). Various hormones can change ventilatory response to CO2 as well (Lambertsen, 1964). Progesterone, for instance, induces a shift of the ventilation-pCO2-response curve to the left, but can also increase RCO2 (Lambertsen, 1964).
It seems that ventilatory response to CO2 is genetically determined (Leitch et al. 1976). By means of twin studies it was found that the most powerful genetic determinant of the

ventilatory response to CO2 is probably tidal volume, while respiratory frequency sensitivity seems more environmentally determined (Arkinstall et al., 1974).

1.2.4 Acid-base balance

(Bernards & Bouman, 1979; Schmidt & Thews, 1980)

This section will address some fundamental definitions and ideas concerning acid-base status of the blood in a simplified manner. One of the most important parameters of blood acidity is the pH, which is defined as -log [H+]. Normal arterial values range from 7.37 to 7.43, with an average pH of 7.4. Values below the normal range are referred to as acidosis, while alkalosis refers to pH values exceeding the normal range. The following compounds contribute to the blood buffering capacity for acid-base disturbances:

1. bicarbonate in plasma and erythrocytes 53%
2. phosphate 5%
3. hemoglobin 35%
4. plasma protein (especially albumin) 7%

In normal circumstances the concentration of basic buffer anions is approximately 48 mmol/liter. The base-excess is then defined as zero (BE=0). Normal values for base-excess are between -2 and +2 mmol/liter. The most influencing buffer is the bicarbonate (HCO3-) buffer. HCO3- is in a dynamic equilibrium with CO2:

$$CO2 + H2O \leftrightarrow H2CO3 \leftrightarrow H+ + HCO3-$$

The acid-base status can be influenced and regulated by respiratory and metabolic mechanisms. Alterations in pH as a consequence of metabolic factors, will rapidly (partially) be compensated by changes in respiration. Respiratory disturbances are partially compensated by metabolic mechanisms, but this process is much slower (6 to 72 hours) (Krapf et al., 1991). Metabolic compensation occurs in the kidneys by regulating H+ and HCO3- blood concentration. In the cerebrospinal fluid and brain tissue there are additional compensation mechanisms, resulting in an almost complete compensation of chronic respiratory acid-base disturbances (Nilsson & Busto, 1973; Kogure et al., 1975).
Hyperventilation, inducing decreased pCO2 and increased pH, results in a state of respiratory alkalosis. When this lasts for a prolonged period, metabolic compensation mechanisms will induce a decrease in blood HCO3- and, consequently, reduced base-excess. As HCO3- contributes to the buffering mechanisms of the blood, this means that the buffering capacity for acid-base disturbances will be decreased. In other words, chronic hyperventilation leads to reduced blood buffering capacity. In this situation, CO2 changes result in greater pH changes than under normal circumstances. Once chronic hyperventilation is in place, it can be retained by relatively few deep breaths (Salzman et al., 1963; Van den Hout et al., 1990).

1.3 RESPIRATORY ASPECTS OF PANIC DISORDER

1.3.1 Respiration in panic disorder.

Respiratory symptoms like dyspnea and smothering sensations are among the most prominent physical features of panic. Some authors have even argued that respiratory phenomena such as hyperventilation are an essential factor in the origin of the anxiety of a panic attack (Hibbert, 1984; Ley, 1985). One of the observations which has led to this conviction is the symptomatic overlap with the "hyperventilation syndrome" (HVS). This syndrome includes symptoms like breathlessness, "air hunger" or suffocation, precordial pain/tightness, paresthesias, dizziness, faintness, palpitations, derealisation, aerophagy, and cold extremities; many of these are believed to be a consequence of decreased arterial pCO2 (Lum, 1976). Methods, used to diagnose HVS include structured interviews and the "hyperventilation provocation test" (HVP), which is based on the recognition of HVP induced symptoms as similar to those occuring in daily life. With both these methods it has been shown that many PD subjects can also be diagnosed as HVS patients. De Ruiter et al. (1989) reports a diagnostic overlap with HVS of 48% for PD without agoraphobia and 83% for PD with agoraphobia, while 82% of generalized anxiety disorder patients were diagnosed as HVS subjects.
These findings could suggest that hyperventilation and other respiratory disturbances are important in panic, but they give no direct evidence. In order to approach this problem systematically it is useful first to ascertain whether objective respiratory disturbances do indeed occur in PD. Thereafter, the influence of possible respiratory abnormalities on the anxiety and other symptoms in PD patients can be considered. Furthermore, it is important to distinguish the situation during panic attacks from the situation in between panic attacks.

RESPIRATION DURING PANIC ATTACKS

Data on objective respiratory disturbances during panic are scarce, as it is a matter of coincidence that a PD patient has a natural panic attack in the laboratory setting, which would allow accurate measurements. In two single case studies, in which blood was sampled during a spontaneous panic attack, a clear respiratory alkalosis was found (Salkovskis et al., 1986; Griez et al., 1987a). A few years ago, a new method of CO2 measurement, permitting continuous ambulant transcutaneous CO2 registration, was introduced in panic research (Pilsbury & Hibbert, 1987). Unfortunately, there is no general agreement on the validity of this method, with one of the major points of controversy being the sensitivity for measurement of relatively small and short lasting CO2 changes. Using this technique, Hibbert & Pilsbury (1988) found decreased pCO2 levels during some, but not all panic attacks. Garssen & Buikhuisen (1991), applying the same method, found no signs of hyperventilation in any of their registered panic attacks. In conclusion, the results of various studies on the occurence of hyperventilation during panic attacks seem inconsistent, but suggest that hyperventilation can accompany

at least some but not all panic attacks.
It has been suggested that hyperventilation plays an essential role in panic (Hibbert, 1984; Bonn et al., 1984; Ley, 1985). According to Ley (1985), the symptoms of hyperventilation, especially dyspnea, precede the experience of anxiety. These symptoms might lead to anxiety by means of the principle of "catastrophic misinterpretation" (Clark, 1986) or "fear of symptoms" (Van den Hout et al., 1987). A panic attack would then consist of a synergistic interaction between hyperventilation and anxiety (Ley, 1985). Ley also suggests that an increase in pH in the range of 7.4 to 7.6 and/or a decrease in pCO2 in the range of 40 to 20 mmHg lead to relatively small increments in symptoms, whereas increases in pH beyond 7.6 and/or decreases in pCO2 beyond 20 mmHg results in a dramatic changes in physical symptoms (Ley, 1986).
At first glance this hyperventilation mediated explanation of panic seems quite convincing. However, there are various indications that this concept is questionable. First, as already mentioned, not all panic attacks seem to be accompanied by hyperventilation (HV).
A second argument comes from a study of Hibbert & Pilsbury (1989) in which they compared panic attacks accompanied by HV with those not accompanied by HV, as assessed with transcutaneous CO2 monitoring. The groups could not be distinguished from one another on the basis of their usual symptoms or the HVP test, and there was no clear association between absolute levels of pCO2 and the nature of symptoms. The anxiety levels of hyperventilators were even lower than those of non-hyperventilators. In other words, they found no indications that HV causes panic attacks or contributes to their severity.
Further evidence against the role of HV in PD comes from studies of Roll (1987) and Hornsveld et al. (1990). Patients suspected of HVS were asked to perform a HVP test and a mental load task (Stroop Colour naming test). Although severe hypocapnia occured during HVP, while during the STROOP test subjects remained normocapnic, approximately the same number of patients recognized symptoms during HVP as during the STROOP test. Thus, HVP positive response to the HVP (i.e. symptom recognition) should not be taken as evidence that patients actually hyperventilate during panic attacks.
Another approach using voluntary hyperventilation is to use it as a provocation test for panic attacks. If the synergistic interaction between hyperventilation and anxiety during a panic attack exists, HVP would be expected to induce panic in PD patients. Data on this matter are however inconclusive. Gorman et al. (1984a, 1988) reported that only a few PD patients (approximately 25%) got a panic attack during HVP. Other reports found considerable higher rates of panic (up to more than 50%) during hyperventilation provocation (Garssen et al., 1983; Holt & Andrews, 1989a; Maddock & Carter, 1991). This matter seems therefore as yet unresolved. Comparing these reports is, however, difficult as the methodologies were different in the various studies. Furthermore, cognitive factors, which have been shown to be of considerable influence on anxiety during HVP (Margraf & Ehlers, 1987), differed. An additional problem is that HVP does not distinguish symptoms which are produced by hypocapnic alkalosis from those produced by the mechanical discomfort and fatigue of fast breathing. Therefore, in order to obtain the response on hypocapnic alkalosis only, it seems necessary to include a control condition which gives the same respiration movements as in HVP, without influencing blood pCO2. One method for this in the past has been adding CO2 in the air

inspired, but, as will be discussed in the next section, this led to even higher rates of panic than during HVP. Another approach is to increase the dead space of the airways artificially by connecting a tube to a mask which is put over the mouth and nose, and then to perform the same respiratory movements as during HVP, resulting in unchanged pCO2. This latter method was used in chapter 2.2.1 and 2.2.2.

RESPIRATION IN BETWEEN PANIC ATTACKS

Research on the occurence of respiratory disturbances in PD patients in the absence of a panic attack is easier than during a panic attack, and therefore it is not surprising that there is much more data concerning this topic. The interpretation of the results does however raise various problems. Many measurements were performed just before subjects were undergoing other, sometimes rather frightening tests, which might have induced considerable anticipatory anxiety, while the level of anxiety was not always assessed. The use of medication differs beween various experiments, and sometimes it is unclear whether, what kind, or in what dosages medication was taken. In addition, the experimental groups have not always been equally defined and selected. Finally, the methods of assessment of various parameters differ, for example, pCO2 measurements being derived from end-tidal expiration air, venous blood, or arterial blood. Given these differences in methodolgies the following summary of the results of various studies should be regarded with some caution.

PD patients tend towards thoracic breathing (Lum, 1976; Beck & Scott, 1988), which may lead to inefficient respiration. It requires considerable muscle effort (Rousos & Macklem, 1982), which may contribute to their feeling of breathlessness (Cohn, 1983; Jones et al., 1990).

Most studies found no differences in respiratory rate (RR) at rest between PD patients, and other anxiety disorder patients or normal controls (Gorman et al., 1988; Pain et al., 1988; De Ruiter et al., 1989; Holt & Andrews, 1989b; Van den Hout et al., 1991), although a few reports describe higher RR in PD/agoraphobics than in normals (Ley, 1985; Maddock & Carter, 1991) or higher RR in PD than in other anxiety disorders (Holt & Andrews, 1989b). Concerning the tidal volume less data are available, but at least 2 studies found higher tidal volumes in PD than in normals (Pain et al., 1988; Gorman et al., 1988). The minute volume has been reported to be either higher in PD than in normals (Pain et al., 1988), or approximately equal to normals (Gorman et al., 1988; Holt & Andrews, 1989b).

Although the majority of studies found lower pCO2 in PD patients than in normals (Liebowitz et al., 1985; Rapee, 1986; Gorman et al., 1986; Papp et al., 1989b; Van den Hout et al., 1991), a substantial number of reports found no difference in pCO2 between PD patients and normals (Pain et al., 1988; Holt & Andrews, 1989b; Maddock & Carter, 1991). Of 4 reports comparing pCO2 in PD with other anxiety disorders, 3 found no difference in pCO2 (De Ruiter, 1989; Holt & Andrews, 1989b; Van den Hout, 1991), whereas 1 found lower pCO2 in PD than in generalized anxiety disorder (Rapee, 1986), although in the latter study PD subjects also had higher heart rates, suggesting a higher level of arousal. The suggestion that low baseline pCO2 is best understood as a common concomittant of arousal, and most likely not as being specifically related to PD, is supported by a study of Van den Hout et al. (1991). They

found that PD, other anxiety disorder patients and normals had similar responses in increases in distress, RR, variability of PET CO2 and decreases in PET CO2 on watching an exciting film and during fearful imagination. At baseline the only difference between the 3 groups was found for PET CO2, both anxiety groups having lower values than normals. Lower pCO2 in PD might therefore merely be a consequence of increased arousal.
Regarding the clinical significance of these pCO2 data in the various reports, it seems that in the vast majority of PD patients pCO2 values are probably still too high to induce physical symptoms of great importance (Ley, 1986). However, when subjects continuously have a somewhat decreased pCO2, it is possible that, as a result of metabolic compensation, the buffering capacity of their blood decreases, as explained in chapter 1.2.4. In that situation a relatively small increase in arousal, resulting in relatively small overbreathing, would already lead to considerable pH changes, thus possibly inducing a relatively great increase in physical symptoms. Therefore, it is of interest to know whether PD patients actually do chronically hyperventilate to an extent that reduces blood buffering capacity, or, in other words, whether PD patients have decreased HCO3- or base-excess values. Data on chronic hyperventilation are however scarce and inconsistent. One study, using venous blood found lower HCO3- values in PD than in normals (Gorman et al., 1986), whereas another, using arterial blood, found no differences in HCO3- between PD patients and normals (Papp et al., 1989b). Margraf (1990), using arterial blood, found base excess values all in the normal range in a group of PD patients. As the possible occurence of chronic HV might be of considerable interest, as pointed out above, further studies on this matter seemed warranted (Chapter 2.1.1).

1.3.2 Inhalation of CO2 in panic disorder.

In the previous section attention was mainly focused on the occurence and effects of decreases in blood pCO2 in PD. However, in the last decade it has become clear that, at least in most studies, inhalation of CO2, which has the opposite effect on blood pCO2 and pH as hyperventilation, leads to higher rates of panic attacks in PD than experimentally induced respiratory alkalosis. After a brief historical background this section will summarize these initially rather surprising and unexpected findings concerning CO2 provoked panic.
The first use of CO2 in medicine probably occured in the 19th century when Hickman promoted it as an analgesic (Leake, 1973). Although it apparantly was effective, CO2 never gained ground in anaesthesiology. In 1929 CO2 inhalation was for the first time introduced in psychiatry as a treatment for "dementia precox, manic depressive insanity and involutional melancholia"; however the results were shortlived (Loevenhart et al., 1929). The interest for CO2 reappeared around 1950 with various studies on the effect of CO2 in anxiety. Cohen & White (1951) reported that rebreathing CO2 caused anxiety attacks in patients suffering from "neurocirculatory asthenia". On the other hand, Meduna (1955) found clinical improvements in various neurotic disorders, including "anxiety neurosis". His results obtained wide attention and even led to the foundation of the "Carbon Dioxide Research Association". After a few years the enthusiasm for the use of CO2 faded again, although a few behavioral therapist continued to use single

inhalations of CO2 for its relaxing and anxiolytic effects (Wolpe, 1958; Slater & Levy, 1966; Ley & Walker, 1973).
It was not until the early 80's that CO2 inhalation regained attention in psychiatry again, when 2 groups independently started using CO2 in panic research.
In an experiment by Gorman et al. (1984a) inhalation of 5% CO2 for a prolonged period up to 20 minutes was used as a control for hyperventilation provocation. Thus far, it was not clear whether the anxiety attacks provoked by the HVP were a consequence of the induced respiratory alkalosis or of the fatigue and discomfort of breathing fast. With 5% CO2 the minute volume increases approximately 300%, while it does not induce decreases in blood pCO2 (blood pH and pCO2 appeared to remain approximately the same). The gas mixture was administered using a canopy as described in 1.2.3. To their surprise, inhaling CO2 provoked panic attacks more frequently (7 out of 12) than HVP (3 out of 12) in PD patients, the panic rate during CO2 inhalation being only slightly lower than during lactate infusion (8 out of 12). Normal controls were hardly affected in either challenge test. An extension of this experiment substantiated these results (Gorman et al., 1988).
Meanwhile, Griez & Van den Hout had started applying 1 or 2 inhalations of a gas mixture of 35% CO2 and 65% O2, with inhalations of air as a control condition. Originally their hypothesis was that this method would reduce anxiety symptoms as in the experiments of Wolpe (1958), Slater & Levy (1966) and Ley & Walker (1973). However, not only did they fail to replicate these findings (Griez & Van den Hout, 1982; Van den Hout & Griez, 1982), they found that one inhalation of 35% CO2/65% O2 induced physical symptoms in healthy volunteers that were similar to those during panic attacks (Van den Hout & Griez, 1984; Griez & Van den Hout, 1983). Later, when administered to PD patients, the single vital capacity inhalation of 35% CO2 also appeared to provoke high anxiety, in contrast to healthy controls, who only experienced a slight increase in subjective distress (Griez et al., 1987c). The induced phenomena were quite similar to those of real life panic. Usually panic symptoms disappeared within a minute.
The finding that CO2 inhalation causes panic in PD patients, in contrast to healthy controls, has been replicated by Woods et al. (1988), using prolonged inhalation of 5% CO2, Fyer et al. (1987), using inhalations of 35% CO2, and Rapee et al. (1986), using inhalations of 50% CO2. Woods et al. (1988) also demonstrated that prolonged inhalation (up to 15 minutes) of 7.5% CO2 in healthy subjects may give similar effects on anxiety and symptoms as 5% CO2 in PD patients, possibly indicating that PD patients have a lower threshold for the activation of the CO2 anxiogenic mechanisms (Woods et al., 1988).
When applying the "usual" procedures (prolonged inhalation of 5% CO2 or one vital capacity inhalation of 35% CO2), there are strong indications that CO2 induced anxiety is specifically related to PD and does not (or much less) affect subjects suffering from other anxiety disorders. Gorman et al. (1988) found that none of the 12 subjects in a group with patients suffering from social phobia, obsessive-compulsive disorder or generalized anxiety disorder panicked during 5% CO2 inhalation (against 12 out of 31 PD patients and 1 out of 13 healthy controls). The 35% CO2 model has been shown to differentiate between PD and obsessive-compulsive disorder subjects, who had responses similar to these of normals (Griez et al., 1990a). Holt & Andrews (1989a) reported that inhaling 5% CO2 (for up to 8 minutes) resulted in greater "fear of impending doom"

and higher panic rates in PD patients with agoraphobia (56%) or without agoraphobia (36%) than in social phobia (16%) and generalized anxiety disorder (0%). In their experiment panic rates during CO2 inhalation were only slightly higher than during HVP (48% in PD with agoraphobia, 20% in PD without agoraphobia, 0% in social phobia and 0% in generalized anxiety disorder). A drawback in this study is however that cognitive variables differed between the groups in that subjects were told that only individuals who suffer from panic attacks might expect to experience symptoms of panic.
It has been argued that an increased vulnerability to CO2 inhalation is merely a consequence of increased baseline arousal as opposes to being specifically related to PD (Ehlers et al., 1986). However, the 35% CO2 model differentiated between a PD group and a group with other anxiety disorders with similar baseline anxiety levels (Griez et al., 1990b).
Although the reliability and specificity of the CO2 challenge tests require further investigation, they are quite promising methods for experimental panic. Compared to other challenge tests like lactate infusion, CO2 inhalation is relatively simple, safe and noninvasive. The 35% CO2 model has the advantage over prolonged inhalation of 5% CO2 that it is less time consuming.
The mechanisms behind CO2 induced panic in PD patients have not yet been clarified, although there are various speculations. In chapter 3 the relationship between CO2 and panic has been approached from a neurophysiological perspective. Other, psychological theories have been discussed in chapter 1.1.3. As has been pointed out in these chapters, thus far most theories concerning the pathogenesis of PD seem consistent with the finding that CO2 can provoke panic in PD patients. A further analysis of the CO2 induced panic symptom profile (chapter 2.2.3) may however give more information about the mechanisms behind CO2 provoked panic and possibly lead to stronger indications concerning the pathogenesis of PD.

1.3.3 Ventilatory response to CO2 in panic disorder.

One of the explanations for the emotional vulnerability to CO2 in PD is that PD patients have hypersensitive medullary CO2 chemoreceptors (Carr & Sheehan, 1984; Gorman et al., 1988). Carr & Sheehan (1984) have speculated that this hypersensitivity might be the result of a defect in the intracellular redox regulation system. This hypothesis has however never been supported by experimental evidence. They also suggest that the course of events during a panic attack may be as follows:

> medullary chemoreceptor pH drop and/or inapproriate triggering of respiratory cascade -> arousal/anxiety -> (further) increase in ventilation -> hypocapnia -> alkalosis -> decrease in cerebral floodflow -> central ischaemia and (further) drop in central pH ...

This model would also explain the role of hyperventilation during panic attacks. In addition, the postulate of hypersensitive chemoreceptors could explain the possible occurence of chronic hyperventilation in PD as well (Gorman et al., 1988).
If the hypothesis that hypersensitive chemoreceptors are responsible for the emotional

vulnerability to CO2 in PD is correct, it is expected that the ventilatory response to CO2 (RCO2; chapter 1.2.3) is higher in PD than in other anxiety disorders and in healthy controls. Research on ventilatory response to CO2 in PD has however shown conflicting results. On the one hand, Lousberg et al. (1988), using Read's rebreathing technique, reported higher RCO2 values in 19 PD patients than in 14 healthy controls. With the steady-state canopy procedure Papp et al. (1989a) found greater RCO2 in 7 male PD subjects than in 5 male healthy controls. On the other hand, Woods et al. (1986), using Read's rebreathing technique, found similar responses in PD and normals. Although Pain et al. (1988) found no difference in RCO2 between PD and healthy controls either with Read's rebreathing technique, he did find a lower sensitivity with reference to the tidal volume component in PD than in normals, while the sensitivity with reference to the respiratory frequency component proved to be higher in the PD group than in the control group.
Concerning the extrapolated pCO2 intercept, indicating the hypothetical pCO2 providing zero stimulus to ventilation, 2 reports found no difference between PD and healthy controls (Woods et al., 1986; Lousberg et al., 1988).
Summarizing, the results of various studies on RCO2 seem inconsistent, and therefore further research on RCO2 is needed. In order to investigate whether possible increased RCO2 is specifically related to PD, it should also include measurement of RCO2 values in other anxiety disorders (chapter 2.3.2).
Breath-holding induces endogenous CO2 accumulation, and may be considered as a rough method of testing the CO2 chemoreceptors, although the possible influence of voluntary control should be acknowledged. Various versions of breath-holding tests have been used in disorders other than PD, in which cases it was intended to be a test of autonomic failure (Bannister, 1988/1989) or functional cardiovascular disease (Friedman, 1945, 1947). Mäntysaari (1984) found that subjects with "neurocirculatory dystonia" tended to have a lower ratio of breath-holding times after and before hyperventilation. Patients with chest pain and normal ECG, and with a positive hyperventilation provocation test have been demonstrated to have shorter breath-holding times than healthy controls (Bass et al., 1990).
Research on breath-holding in PD (chapter 2.3.1), especially when contrasted with other anxiety disorders, is of interest, as it may give indications of a disregulation in respiratory control in PD. In addition, if breath-holding appears to distinguish between PD and other anxiety anxiety disorders, it might serve as an extremely simple test supporting the diagnosis of PD in patients with anxiety disorders.

1.3.4 Link with respiratory diseases?

PD and some diseases affecting the respiratory system show a considerable overlap in symptomatology. Common to both are dyspnea, smothering sensations and choking. Furthermore, Kinsman et al., (1973) have found that 42% of asthmatic patients report a frequent occurence of symptoms from a panic/fear cluster. Disturbances in respiratory control, such as hyperventilation, have been reported to occur frequently in PD (Hibbert & Pilsbury, 1988) as well as in asthma (McFadden et al., 1968).
In addition to this symptomatic overlap there are indications of increased co-morbidity of diseases affecting the respiratory system and PD. In one study it has been reported,

that 24% of 50 asthmatics could also be diagnosed as PD patients (Yellowlees et al., 1987). In a later study Yellowlees et al. (1988) found that 12% of 49 asthmatic patients also met the panic disorder DSM-III criteria. Karajgi et al. (1990) reported that in 50 outpatients with stable chronic obstructive pulmonary disease there was a lifetime prevalence rate for PD of 8% as assessed by the DSM-III-R criteria. These rates are higher than the lifetime prevalence rates for PD of 1-5%, which are found in the general population (Robins et al, 1984; Kaplan & Sadock, 1988).

There are several limitations to these studies. A difference of only 1 subject in each of these reports would already have made a difference of 2%, while it is not always very easy to distinguish a "genuine" panic attack from increases in anxiety directly associated with pulmonary disease. In addition, these studies did not assess whether subjects with PD had panic attacks before or after pulmonary pathology began.

Nevertheless, the results are quite intriguing as they could indicate a possible pathophysiological link between PD and (some) respiratory diseases. Therefore, it seemed of interest to further investigate the relationship between PD and respiratory pathology (chapter 2.3.3).

1.4 OVERVIEW OF EMPIRICAL STUDIES

As hyperventilation has been postulated to be one the most essential mechanisms of panic (Hibbert, 1984; Ley, 1985), it was of interest to investigate whether hyperventilation did indeed occur in PD and, if so, whether it played an essential pathogenetic role in panic.
The results of various studies have indicated that hyperventilation can accompany at least some panic attacks, although very likely not all (Salkovskis et al., 1986; Griez et al., 1987a; Hibbert & Pilsbury, 1988; 1989; Garssen & Buikhuisen, 1990).
The possible occurence of hyperventilation in PD patients in the absence of a panic attack has been extensively studied, most reports indicating a slightly decreased pCO2, various others finding no difference between PD patients and healthy controls (for an overview see chapter 1.3.1). One of the possible consequences of continuous decreased pCO2 could be a decreased buffering capacity of the blood. In this situation relatively small pCO2 changes would induce relatively great changes in blood pH, thus increasing the chance of experiencing physical symptoms. However, it is as yet unclear whether PD subjects do chronically hyperventilate, as data are scarce and inconsistent, while the results were not always compared with anxiety disorders other than PD (Gorman et al., 1986; Papp et al., 1989b; Margraf et al., 1990). Therefore the study described in chapter 2.1.1 was conducted. No difference in arterial base excess values were found between 18 PD, 12 other anxiety, and 18 healthy control subjects, indicating that there was no reduced buffering capacity in either group. There were no clear indications of clinically significant decreased pCO2 values either.
The second question addressed was whether the respiratory alkalosis, which can occur during panic attacks, plays a pathogenetic role during panic. If there was a synergistic interaction between anxiety and physical symptoms induced by respiratory alkalosis during a panic attack (Hibbert, 1984; Ley, 1985), one would expect a considerable increase in anxiety during experimental hypocarbia in PD patients. A problem with the usual hyperventilation provocation (HVP) test is that it does not distinguish symptoms which are produced by hypocapnic alkalosis form those produced by the mechanical discomfort and fatigue of breathing fast and deep. Therefore, it was decided to include a control condition, in which experimental subjects performed the same respiration movements as in HVP, but remained normocapnic. This was done by connecting a tube to the mask which subjects were breathing through, thereby artificially increasing the "dead space" of the airways. In the experiment described in chapter 2.2.1 11 PD patients and 8 normal controls underwent a HVP test, which reduced end tidal pCO2 to less than half of its initial value, and the above mentioned "fake" hyperventilation as a control condition. It was found that experimental hypocarbia induced no clinically significant increase in anxiety in either group. However, it could be argued that many factors other than hypocarbia (as for instance the nature of instructions) may have influenced the level of anxiety reported by the subjects in this study. Therefore, it was decided to compare, in strictly standardized circumstances, the effects of experimental hypocarbia with the effects of the 35% CO2 challenge test, which is a fairly well established method of panic provocation. This experiment is described in chapter 2.2.2, in which the anxiogenic effects of experimental hypercarbia and hypocarbia were

assessed in 12 PD and 11 healthy control subjects. Corresponding with our expectations, it was found that the induced anxiety during the 35% CO2 challenge in PD patients was significantly higher than during the other 3 conditions (35% CO2 in normal controls, and HVP in both PD subjects and controls), there being no difference between these latter 3 conditions.

As both CO2 inhalation and hyperventilation may produce panic like symptoms, but only CO2 was found to induce considerable anxiety in PD patients, it seemed of interest to investigate which specific symptoms correlated best with CO2 induced anxiety in PD patients, and, in addition, which symptoms differed between CO2 inhalation and HVP in PD. This study, which is described in chapter 2.2.3, revealed that CO2 provoked anxiety correlated best with respiratory symptoms in 20 PD patients, while the same symptoms appeared to be significantly more severe during the 35% CO2 challenge than during HVP.

This apparent importance of respiratory symptoms in (experimental) panic, and the emotional vulnerability of PD patients to CO2 loading, may indicate a possible relationship between panic and respiratory disregulation. Further research on this was therefore warranted. A simple, although rather rough, method to investigate respiratory control is the assessment of breath-holding capacity, although it should be acknowledged that this test may be influenced by factors other than respiratory physiology. However, as breath-holding needs almost no equipment and is very easy to apply, it was decided to investigate whether breath-holding could serve as a simple test supporting the diagnosis of PD in patients with anxiety disorders. In the experiment in chapter 2.3.1 14 PD patients, 14 patients suffering from other anxiety disorders, and 14 healthy controls underwent a breath-holding test. It was hypothesized that PD patients would have shorter breath-holding times than other anxiety and normal subjects. It was found that, although breath-holding capacity appeared to be significantly lower in PD patients than in normal control subjects, other anxiety disorder patients also tended to have lower breath-holding times than normals. There was merely a trend towards lower apnea times in PD than in other anxiety using a one tailed t-test.

A more sophisticated and accurate measure of respiratory control is the assessment of the ventilatory response to CO2, which is used in the experiment described in chapter 2.3.2. If a disturbance in respiratory control, such as hypersensitive medullary CO2 chemoreceptors (Carr & Sheehan, 1984; Gorman et al., 1988) is specifically related to PD, RCO2 values would be expected to be higher in PD than in OCD and healthy control subjects. No difference in RCO2 was found between 15 PD, 15 obsessive-compulsive disorder, and 15 healthy control subjects. The tidal tidal volume and frequency components of the ventilatory response showed no difference between the groups either. However, the pCO2 intercept, indicating the hypothetical pCO2 value corresponding with zero ventilation appeared to be significantly lower in the PD group than in the normal control subjects, although this latter finding should be regarded with some caution, as indicated in 2.3.2.

The importance of respiratory symptoms in PD and the resemblance in symptomatology between PD and some respiratory diseases, together with the findings of increased prevalence of PD in asthmatic/COPD patients (Yellowlees et al., 1987, 1988; Karajgi et al., 1990) might point to some association between PD and respiratory diseases. These considerations have led to the pilot study in chapter 2.3.3, which assessed current and past frequency of respiratory diseases in 30 PD, 30 obsessive-compulsive disorder

(OCD) and 30 eating disorder (ED) patients. Lifetime and childhood prevalence of respiratory disorders appeared to be significantly higher in PD than in either OCD or ED. Point prevalences showed no differences.

CHAPTER 2: EXPERIMENTS

2.1

DO PD PATIENTS HYPERVENTILATE?

2.1.1 No chronic hyperventilation in panic disorder patients

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ABSTRACT

Arterial blood gases were measured and base excess calculated in 18 non-panicking panic disorder (PD) patients, 12 subjects suffering from other anxiety disorders and 18 normal controls. There was neither chronic nor clinically significant acute hyperventilation in either group.

INTRODUCTION

It has been well established that, at least in some cases, panic disorder (PD) patients hyperventilate during their attacks (Salkovskis et al., 1986; Griez et al., 1987a; Hibbert and Pilsbury, 1988). This acute respiratory hypocarbia has been held responsible for many of the symptoms during panic attacks (Hibbert, 1984; Ley, 1985).

PD patients often experience physical symptoms in between panic attacks as well, and it is tempting to attribute these symptoms to chronic hyperventilation. If this persistent respiratory alkalosis does indeed occur, it will induce negative base excess (Schmidt and Thews, 1980), resulting in reduced buffering capacity of the blood. A relatively small pCO2 disturbances would then be sufficient to induce considerable pH alterations. In other words, a few extra breaths (as well as externally induced hypercapnia) would provoke more symptoms in these chronic hyperventilators than in non-chronic hyperventilators.

Data on chronic hyperventilation in PD has shown conflicting results. In venous blood Gorman et al. (1986) found on average a lower pCO2 and bicarbonate (HCO3-), and higher pH in PD patients than in normal controls, suggesting mixed chronic and acute respiratory alkalosis. In contrast, when arterial blood was taken, the same group of investigators found values which were more consistent with acute but not chronic hyperventilation (Papp et al., 1989). In both studies however, measurements occured shortly before lactate infusions, and thus the influence of considerable anticipatory anxiety could not be excluded.

When patients were investigated in less threatening circumstances during arterial blood sampling, no differences in pCO2, pO2, pH, and base excess were found between patients with PD, bronchial asthma, or depression (Margraf, 1990).

Patients suffering from other anxiety disorders may also experience similar symptoms to those occurring in PD subjects in between their panic attacks. It could be argued that hyperventilation is a common phenomenon in anxiety patients instead of being specifically related to panic disorder. It would therefore be of interest to compare blood gases and base excess in PD subjects with those in patients suffering from other anxiety disorders.

In the present study arterial values of pCO2 and base excess were measured in a group of non-panicking PD patients, a group of subjects suffering from other anxiety disorders and a group of normal controls. Undergoing an arterial puncture could induce some stress, leading possibly to slight hyperventilation. If this were to happen at all in the PD group, it would be controlled for by inclusion of the group consisting of other anxiety disorders. Our hypothesis was that neither chronic nor acute hyperventilation would be found in either group.

METHODS

Subjects

The 30 anxiety subjects were patients who had been referred to the Academic Anxiety Center of the Mental Hospital Vijverdal. All patients were diagnosed by experienced clinicians using the DSM-III-R criteria (American Psychiatric Association, 1987).
The patients were divided into two groups.
The first one consisted of 18 PD patients, 9 men and 9 women, with a mean age of 38.6 $\pm$ 7.1 years. None of the women were post-menopausal.
The second group, 6 men and 6 women, with a mean age of 34.1 $\pm$ 12.4 years, included 6 obsessive-compulsive disorder patients, 4 social phobics and 2 generalized anxiety disorder patients. In this group 2 women were post-menopausal.
The 18 healthy control subjects were 9 men and 9 women, with a mean age of 33.4 $\pm$ 5.8 years. None had either past or current psychiatric problems. None of the women were post-menopausal.
There were no significant differences between the 3 groups in age (ANOVA, $F=1.974$, $df=2,45$, $p=0.151$) or gender distribution, each group consisting of 50% men and 50% women.
The subjects were all in good physical health and not
under current psychiatric treatment. They were medication free for at least 2 weeks, except for incidental use of low dosages of benzodiazepines (equivalent to $\leq$ 10 mg diazepam/day). They were asked to refrain from food, coffee, tea and smoking for at least 2 hours and alcohol for at least 8 hours preceding the puncture.
None of the subjects had a panic attack at the moment blood was sampled.

Procedure And Apparatus

Blood was obtained by means of a puncture in the radial artery, using the Concord "Arterial Blood Sampling System". Measurement of pH, pCO2 and pO2 took place within 5 minutes using a 1312 Blood Gas Manager of Instrumentation Laboratory Ltd. Assessment of Hb, necessary for calculation of base excess, took place within a period of a week of the arterial punction.
The following formula was used for calculation of HCO3-:

$$\log[HCO3\text{-}] = pH + \log pCO2 - 7.604$$

Base excess was calculated by:

$$(1-0.014)[Hb])([HCO3\text{-}] - 24 + (1.43[Hb]+7.7)(pH-7.4))$$

Data Analysis

One way ANOVA's were performed for base excess and pCO2. The values of pH, pO2 and HCO3- were analysed in a similar way. When significant effects were found,

corresponding t-tests were carried out. The values of pH were also tested by means of non-parametric tests.

RESULTS

Table 1 shows the values of pCO2, pH, pO2, base-excess and bicarbonate (HCO3-) in the 3 groups.

Table 1. Measured and calculated parameters in the three experimental groups (values are expressed as means ± standard deviation).

	PD patients (n=18) 9 men 9 women	other anxiety disorder patients (n=12) 6 men 6 women	healthy controls (n=18) 9 men 9 women	difference between the three groups (ANOVA)
age (years)	38.6 ± 7.1	34.1 ± 12.3	33.4 ± 5.8	N.S.
pCO2 (kPa)	4.999 ± 0.364	5.393 ± 0.348	5.159 ± 0.349	p=0.017
pH	7.418 ± 0.020	7.399 ± 0.019	7.411 ± 0.015	p=0.047
pO2 (kPa)	12.61 ± 1.73	11.74 ± 1.43	12.51 ± 1.04	N.S
base excess (mmol/l)	0.715 ± 1.187	1.099 ± 1.112	0.931 ± 0.768	N.S.
HCO3- (mmol/l)	24.46 ± 1.26	25.28 ± 1.19	24.84 ± 1.02	N.S.

One way ANOVA for pCO2 revealed a significant difference ($F=4.437$, $df=2,45$, $p=0.017$). Corresponding t-tests of pCO2 values showed no significant difference between the PD subjects and normal controls ($t=-1.34$, $df=34$, $p=0.189$). A trend for a differerence for pCO2 was found between other anxiety patients and normals ($t=1.80$, $df=28$, $p=0.082$), while the PD and other anxiety groups significantly differed ($t=-2.95$, $df=28$, $p=0.006$).

One way ANOVA revealed a significant difference for pH between the 3 groups ($F=3.264$, $df=2,45$, $p=0.017$). Corresponding t-tests showed no significant difference in pH between the PD patients and healthy controls ($t=1.05$, $df=34$, $p=0.301$), and a trend for a difference between other anxiety subjects and normals ($t=-1.83$, $df=28$, $p=0.078$), while there was a significant difference between the PD and other anxiety groups ($t=2.31$, $df=28$, $p=0.029$).

Non-parametric tests for pH gave similar results. Analysis by means of Kruskall Wallis revealed a significant difference in pH between the 3 groups ($p=0.0445$). Pairwise

comparisons between the PD subjects and normals showed no significant difference (Mann-Whitney U, p=0.282), while there was a trend for a difference between the other anxiety disorder and normal group (Mann Whitney U, p=0.0513). A significant difference in pH was found between the PD subjects and patients suffering from other anxiety disorders (Mann-Whitney U, p=0.0276).
Analysis by means of one-way ANOVA showed no difference between the 3 groups for pO2 (F=3.077, df=2,45, p=0.233).
No significant difference between the 3 groups was found either with one-way ANOVA for base excess (F=0.552, df=2,45, p=0.597) and HCO3- (F=1.828, df=2,45, p=0.172).
When men and women were analysed separately, similar patterns were found for pCO2, base-excess and HCO3-.
In men pH showed a significant difference between groups with ANOVA, while a trend for a difference was found with Kruskal-Wallis. In women there was no difference in pH between the groups, neither with parametrical nor with non-parametrical tests.
The pO2 values showed no difference between the 3 groups in men, while in women there was a trend for a difference, the value of pO2 being slighlty lower in the other anxiety group.

DISCUSSION

The main purpose of the present study was to investigate whether PD patients chronically hyperventilate. No significant differences in base-excess or HCO3- were found between PD patients, other anxiety disorder patients, and normal controls, indicating that there was no systematic chronic hyperventilation in either group. Actually, only 1 of 18 PD patients, and none of the other subjects had a base-excess value (-2.31 mmol/l) below the normal clinical range of -2 to +2 mmol/l.
These findings imply that the buffering capacity of the blood of PD patients is not reduced. Thus, pCO2 changes, by means of a few extra breaths for instance, will not result in greater pH changes in PD subjects than in other anxiety disorder patients, or healthy controls. In addition, the possible occurence of symptoms in between panic attacks can not be attributed to chronic hyperventilation.
Although base excess is the most reliable parameter for respiratory state over an extended period, the pCO2 gives more information about possible acute hyperventilation at the moment of the puncture. In the present study significant differences were found for pCO2 and pH values. However, there were no significant differences between PD subjects and healthy controls. The differences in pH and pCO2 between the PD subjects and patients suffering from other anxiety disorders hardly seem of any clinical significance. Only 4 of 18 PD patients, none of the other anxiety disorder patients, and 1 of 18 normal control had pCO2 values below the normal clinical range. The lowest pCO2 value measured (4.44 kPa in the PD group) was still too high to induce physical symptoms of any importance (Ley, 1986).
The pCO2 data (and consequently the pH data) should be regarded with some cautioun. It is possible that potential differences are overruled, or alternatively, that non existing differences seem to occur by the mere fact that subjects undergo an arterial puncture. Some subjects tend to experience some anticipatory anxiety preceding blood sampling,

resulting in slight hyperventilation, whereas other subjects tend to hold their breath at the moment of the puncture. Therefore, pCO2 (and pH) values derived from blood obtained by this method may not completely reflect those at rest. The slightly higher pCO2 and lower pH values in the group with other anxiety could then be an artefact. Nothwithstanding these limitations, it seems reasonable to conclude that, in the absence of a panic attack, PD patients do not severely hyperventilate, even during a slightly stressful event.

The present study investigated possible hyperventilation (HV) in between panic attacks. As mentioned above, PD patients can acutely hyperventilate during their attacks. However, the influence of HV on the severity of natural occuring panic attacks seems doubtful (Hibbert and Pilsbury, 1989; Garssen and Hornsveld, 1990). In addition, hyperventilation provocation fails to provoke panic attacks in PD patients (Gorman et al., 1984, 1988; Griez et al., 1988; Zandbergen et al., 1990). These findings taken together suggest that during panic attacks hyperventilation is a consequence rather than a cause of panic.

In contrast, inhalation of CO2, which has the opposite effect on blood pCO2 (Griez et al, 1987b), does induce anxiety in PD patients, at least in the laboratory (Griez et al, 1987c, 1990a, 1990b). The present study suggests that the vulnerability of PD patients to CO2 inhalation can not be attributed to larger pH changes than in non-PD subjects as a result of reduced blood buffering capacity.

In conclusion, the present study showed no clear signs of hyperventilation in between panic attacks in PD patients, while several other reports suggest that, even during panic attacks, hypocarbia is no major causal factor of the anxiety and symptoms of panic. These findings support the suggestion that, in spite of previous speculations, hyperventilation appears to play no major role in the pathogenesis of panic.

ACKNOWLEDGEMENTS

Thanks are expressed to Dr.E.Wouters, pulmonologist, Dr.H.Pennings, resident in pulmonology, and I.Leclerc, research assistant, for their indispensible assistance.

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2.2

ANXIOGENIC ROLE OF HYPERVENTILATION; COMPARISON WITH CO_2

2.2.1 Effects of low pulmonary CO2 on panic anxiety

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Comprehensive Psychiatry, 29:490-497, 1988

Effects of Low Pulmonary CO_2 on Panic Anxiety

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In order to investigate the possible role of hyperventilation in the pathogenesis of panic, 11 panic patients and eight normal controls underwent a hyperventilation provocation test. The word "hyperventilation" itself was not used; the subjects were told the test was meant to measure the amount of carbon dioxide in their expired air. End tidal pCO_2 was reduced to less than half of its initial value, resulting in a significant increase in physical symptoms, both in patients and controls. However, there proved to be no significant increase in subjective anxiety. It is suggested, that hypocarbia alone is not sufficient to provoke anxiety in panic disorder patients.

THERE IS GOOD, CONVINCING EVIDENCE that hyperventilation mechanisms operate during the course of Panic Attacks. Using the well-known procedure of lactate infusion to provoke attacks in Panic Disorder subjects, Gorman et al.[1] demonstrated that experimental panic is attended by a precipitous drop in venous pCO_2 and bicarbonates, indicating acute hyperventilation. Casuistic studies of real-life panic have repeatedly depicted patients as being in a state of hypocapnic alkalosis at the very moment of their panic attacks.[2,3] However, the role of hyperventilation in the chain of events leading to panic is not clearly established. Should hyperventilation be regarded as a cause or as a consequence of panic attacks? A tentative response to this question may be implicitly inferred from the literature on the so-called "Hyperventilation Syndrome."[4-6] This disorder features sudden episodes of hyperpnea, neurovegetative symptoms, and anxiety. A common view postulates that the pathogenesis of this condition has roots in hyperventilation mechanisms, resulting from faulty breathing habits. Hyperventilation precipitates transient alkalotic states which in turn, activate anxiety.[7] The striking similarities between the hyperventilation syndrome and DSM-III criteria of a panic attack, prompted some authors to consider panic disorder as a case of hyperventilation syndrome and hyperventilation as a cause of panic attacks.[8,9]

However, the hypothesis that panic attacks originate in hyperventilation and respiratory alkalosis suffers from several drawbacks. Although there is little doubt that hyperventilation accompanies panic attacks, it has, to the authors' knowledge, never been demonstrated that hyperventilation may cause panic.

On the contrary, it appears that hyperventilation alone is not a sufficient condition to precipitate panic. In several lactate studies, patients were reported to have been hyperventilating right before the beginning of the infusion. Nevertheless, some of these subjects failed to panic.[1,10,11]

Actually, to date, one experiment has shown that when 12 panic disorder patients were asked to hyperventilate sufficiently to induce significant alkalosis, only three

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0010-440X/88/2905-0006$03.00/0

of them went into panic. Unexpectedly, breathing a gas that was 5% CO_2 precipitated a panic attack in seven of them.[12]

It was therefore suggested that panic disorder patients may be more vulnerable to hypercapnia than to hypocapnia. This hypothesis gained strong support from the recent finding that one single inhalation of a 35% CO_2/65% O_2 mixture is as reliable as lactate in eliciting panic anxiety in panic disorder patients. High levels of subjective anxiety were instantaneously induced in all of the 12 patients who were administered the gas but only in one of the 11 normal controls.[13] The 35% CO_2-triggered anxiety appears synchronously with a hypercapnic peak in body fluids.[14]

In sum, newly emerging data cast some doubts on a generally accepted view that hyperventilation and respiratory alkalosis activate anxiety. Nevertheless, a clinical procedure referred to as the "hyperventilation provocation test," is widely being used under the assumption that the symptoms of the hyperventilation syndrome, including anxiety, are reproduced by maneuvering voluntary hyperventilation. This test has even been advocated as a bedside tool for diagnosing a hyperventilation syndrome.[6]

If the above hypothesis is correct, that it is not hypocapnia but hypercapnia that specifically generates anxiety in panic disorder patients, acute hypocapnia, induced by a test of hyperventilation, should have weak effects in these subjects and leave their anxiety level unaffected. The investigators had this hypothesis in mind when, in the present study, they asked a group of panic patients to undergo a hyperventilation provocation test.

METHODS

Subjects

Eleven patients, four men and seven women, with a DSM-III diagnosis of Panic Disorder participated in the study. Their mean age was 39.55 years, ranging from 23 to 61. The mean duration of their illness had been 4.16 years, with a range of 0.25 to 10. At the time of the study, the patients had no other psychiatric or physical diseases, and were not under formal treatment. All were medication-free.

Eight healthy controls, two men and six women, with a mean age of 22.63 years, ranging from 21 to 25, were also included in the trial.

All subjects had to refrain from alcohol and from xanthine-containing beverages during the 12 hours preceding the test.

Procedure

Subjects were told that they would undergo a procedure involving two types of registration of end tidal pCO_2.

In the experimental condition, (hypocapnic hyperpnea), the subject, seated in a comfortable armchair, breathed as deeply as he or she could through an open mask, with a fixed frequency of 20 breaths per minute for four minutes. The control condition (normocapnic hyperpnea) consisted of the same procedure; however, in this case, a tube of approximately 50 cm was connected to the mask. This system maintained the subject in a normocapnic condition, due to the increased dead space. Following a single blind, random order, cross-over design, each participant underwent both conditions with an interval of half an hour in between.

Assessments

During the respiratory challenges, the end tidal pCO_2 was continuously monitored by a Gould Godart MK III capnograph. Immediately before and after each ventilatory test, 14 panic symptoms, according

to the draft of the DSM-III-R[15] were rated by the subjects on a five point scale, ranging from 0 (absent) to 4 (very intense). The total score ranges from 0 to 56. In addition, the subjects expressed their subjective feeling of anxiety on an imaginary scale ranging from 0 (no anxiety at all) to 100 (the worst imaginable experience), (scale for subjective units of disturbance, [SUDS][16]).

RESULTS

All results were analyzed using two tailed *t*-tests. Main capnographic parameters are summarized in Table 1. In the patient group, voluntary hyperventilation reduced mean PET CO_2 to 49.7% of its initial value. After one minute all patients had a PET CO_2 of <3%, which decreased to <2.5% after one more minute. In the normal control group, these latter conditions were met by five out of the eight subjects, while mean PET CO_2 was reduced to 46.3% of its initial value. Tube breathing did not significantly affect PET CO_2.

Table 2 displays the total scores on the panic symptoms checklist. Voluntary hyperventilation elicited a significant increase in panic-like symptomatology, both in patients ($t = 2.716$, $P < .05$) and normals ($t = 3.634$, $P < .02$, there being no significant differences between the two groups ($t = 0.839$, NS). Tube breathing failed to affect the symptomatology in patients ($t = 0.333$, NS) but a trend to more symptoms appeared in normals ($t = 2.311$, $P < .1$). Again, no significant differences were seen between groups ($t = 1.093$, NS). For each subject, a net increase in symptoms was calculated by subtracting the difference score under the normocapnic condition (tube breathing) from the difference score under the hypocapnic condition (hyperventilation). These net increases in symptomatology were significant, both in patients ($t = 3.745$, $P < .01$) and in normals ($t = 2.422$, $P < .05$) with a trend for patients to report more symptoms than normals ($t = 1.873$, $P < .1$).

Table 3 shows the levels of subjective anxiety, as they were reported in SUDS by the subjects. After hyperventilation, anxiety tended to increase both in patients ($t = 1.899$, $P < .1$) and in normals ($t = 1.471$, $P < .2$), with a very slight trend towards a greater change in the patients group ($t = 1.440$, $P < .2$). Tube breathing lacked any effect ($t = 1.179$, 1.009 and 1.125, all NS, for differences in patients, normals and between groups respectively).

A net increase in subjective anxiety was calculated, as described above for somatic symptoms, Trends towards augmented anxiety appeared both in patients ($t = 1.516$, $P < .2$) and normals ($t = 1.978$, $P < .1$) but no significant differences were seen between changes in anxiety of panic patients and in normal controls ($t = 0.881$, NS).

Table 1. Main Capnographic Parameters (in Volume %) (All Differences Patients v Normals are Nonsignificant)

	PET CO_2 (Mean ± SD)			*t*-test (two tailed)	
	Baseline	Final Tube Breathing	Final VHV	Baseline *v* Tube	Baseline *v* VHV
Patients	3.94 ± 0.365	3.92 ± 0.499	1.93 ± 0.290	$t = 0.07$ NS	$t = 12.17$ $P < 0.001$
Normals	4.21 ± 0.617	3.91 ± 0.548	1.91 ± 0.173	$t = 0.73$ NS	$t = 10.19$ $P < 0.001$

Abbreviations: VHV, voluntary hyperventilation, NS, not significant.

Table 2. Total Score on Somatic Symptoms (Means and SD)

	Hyperventilation			Tube Breathing			Net Increase
	Pre	Post	Difference	Pre	Post	Difference	
Patients (N = 11)	9.09 (9.55)	15.18 (9.44)	6.09 (7.09)	9.27 (10.41)	8.82 (7.72)	−0.45 (4.27)	6.55 (5.53)
Normals (N = 8)	0.75 (0.83)	4.50 (3.24)	3.75 (2.73)	0.25 (0.66)	1.63 (1.80)	1.38 (1.58)	2.38 (2.60)

Table 3. Mean (and SD) Level of Subjective Anxiety (in SUDS)

	Hyperventilation			Tube Breathing			Net Increase
	Pre	Post	Difference	Pre	Post	Difference	
Patients (N = 11)	23.73 (16.94)	33.73 (24.93)	10.00 (16.65)	12.27 (9.85)	22.36 (20.28)	4.64 (12.45)	5.36 (11.18)
Normals (N = 8)	0.00	1.00 (1.80)	1.00 (1.80)	1.88 (3.48)	1.25 (2.17)	−0.63 (1.65)	1.63 (2.18)

DISCUSSION

Whether or not placebo corrected, the results are clear. Voluntary hyperventilation gave rise to symptoms resembling those of panic but hardly caused demonstrable changes in subjective anxiety. Both normal controls and panic patients were affected to a quite similar extent.

That voluntary hyperventilation elicited some symptomatology of panic may be easily conceivable if this is related to the more than 50% drop in PET CO_2 which was generated during the challenge. Hyperventilation expectedly caused respiratory alkalosis, and respiratory alkalosis is known to foster autonomic symptons resembling panic.[17] Curiously, a trend towards more symptoms was present after tube breathing in the normal subjects. Inspection of the raw data showed that mainly two subjects account for this result. One of them was already marginally hypocapnic at baseline, and dropped further to 90% of its initial value, while the other, despite the tube equipment, dropped to a PET CO_2 which was 86% of its baseline. It is therefore possible that these individuals did experience a slight alkalotic symptomatology in the control condition. This contamination of the control condition in the group of healthy subjects may also explain the trend which appears in favor of the patients, in the net increase in symptoms. Other explanations could rely on psychological factors, panic patients being possibly more attentive than normals to internal sensations, which they usually fear.

The above analysis showed the increases in subjective anxiety to be not significant. Admittedly, some trends did emerge, suggesting higher SUDS levels upon hyperventilation.

It must however be kept in mind that anxiety was expressed on a subjective scale. Even though these "SUDS" have been reported to correlate satisfactorily with neurovegetative parameters of arousal,[18] some limitations of such a quasi-quantitative system must be taken into account.

First, it might be argued that SUDS are not on an interval scale. Consequently, SUDS data would not be really suitable for parametric statistics. In order to be as conservative as possible, we did use *t*-tests, but nonparametric statistics (sign test) had led to the conclusion that hyperventilation did not at all affect subjective anxiety, whether in normals or in patients.

A second point is the magnitude of the observed changes in anxiety, regardless of their statistical significance. Panic patients had a placebo-corrected increase of 5.36 SUDS, while normals had one of 1.63 SUDS. What may be the clinical relevance of a 5.36 or 1.63 units change on a quite rough 100 point SUDS scale, as has been described above?

In sum, on the basis of the present data, to say that hyperventilation is panicogenic would be a kind of verbal inflation. Voluntary hyperventilation may be unpleasant to many people. It generates autonomic sensations which eventually influence subjective well-being. As pointed out above, panic patients may be more concerned than normals about such internal changes, and given the neutral experimental conditions (there were no specific anxious expectations), the symptoms were diversely interpreted. This could explain the high variance in the SUDS scores observed in the experimental group.

Good experimental models of disease are assumed to differentiate between normals and those with pathology.[19] In the present experiment, hyperventilation

induced no overall demonstrable differences between patients and normals. In particular, the challenge was not not followed by panic in patients. This failure may invalidate hyperventilation alone as a model for panic disorder and disqualify hypocapnia as a specific triggering factor for panic attacks. In contrast, it is striking that one single inhalation of a 35% CO_2 mixture[13,20] or continuous breathing of 5% CO_2[12] clearly succeeded in differentiating panics from controls. Moreover, the mean increase of 40 SUDS that was observed in panic patients after one 35% CO_2 inhalation[13] sharply contrasts with the 5.36 SUDS noted in the present trial. Some tentative models of panic mainly rely on cognitive factors,[21] and it might be argued that the nature of the pretest instructions, referring only to PET CO_2 monitoring, may account for the lack of effect of hyperventilation in the present study.

A comparative study of voluntary hyperventilation and 35% CO_2 inhalation in a single trial with a repeated measures design would therefore be particularly interesting. Worth remembering is that Gorman et al.[12] already found hyperventilation to be a "weak anxiogenic" compared to 5% CO_2 breathing.

CONCLUSIONS

This study was not specifically designed to investigate resting blood gases. However, it must be noted that baseline PET CO_2 did not differ between patients and normals. Both groups were normocapnic. Some authors[1,10,11] have found arguments for panic patients being at rest in a state of respiratory alkalosis, say, hypocapnic. However, in all of these studies, the patients were in threatening surroundings, about to receive a lactate infusion. As Reiman et al.[11] admitted themselves, the hyperventilation was apparently a response to the experimental situation. Findings on resting hypocapnia in panic have been inconsistent[22] and the present observation adds to the evidence that chronic hyperventilation is not a rule in panic disorder.

There is renewed interest in the role of respiratory disturbances in human psychopathology. The provisory conclusion is that no causal relationship has been demonstrated between hyperventilation and panic. The link is probably more complex, and the role of hyperventilation in the genesis of anxiety is probably not that one which was once believed.

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2.2.2 Hypercarbia versus hypocarbia in panic disorder

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Journal of Affective Disorders, 18:75-81, 1990

Journal of Affective Disorders, 18 (1990) 75–81
Elsevier

JAD00668

Hypercarbia versus hypocarbia in panic disorder

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(Received 10 October 1988)
(Revision received 7 February 1989)
(Accepted 30 May 1989)

Summary

In order to compare the panicogenic effects of hypercarbia and hypocarbia in panic disorder (PD), 12 PD patients and 11 healthy controls underwent a 35% CO_2 challenge as well as a hyperventilation provocation test in a random cross-over design. Both anxiety and anxiety symptoms proved to be significantly higher during the 35% CO_2 challenge in PD patients as compared to the response during 35% CO_2 in normals and during hyperventilation in both patients and normals. The results suggest that PD patients are specifically hypersensitive to an increase in pCO_2.

Key words: CO_2; Hyperventilation; Panic disorder; Provocation test

Introduction

The hyperventilation provocation test has become a routine procedure in confirming the diagnosis of 'hyperventilation syndrome' and/or panic disorder (PD). It seems that during voluntary hyperventilation, PD patients recognize many of the symptoms they experience during a panic attack. Therefore, various researchers have concluded that hypocarbia is an important factor in the origin of anxiety in naturally occurring panic and/or hyperventilation (Lum, 1975; Beumer and Hardonk, 1980; Hibbert, 1984; Ley, 1985; Folgering, 1986). It is commonly accepted that, at least in some cases, panic patients do indeed hyperventilate during their attacks. Moreover, three recent studies have demonstrated a state of hypocapnic alkalosis during acute panic (Salkovsis et al., 1986; Griez et al., 1987a, Hibbert and Pilsbury, 1988).

Nevertheless, a few reports (Gorman et al., 1984, 1988) have suggested that the panicogenic capacity of hyperventilation may be smaller than was once believed. In spite of the induction of considerable physical symptoms, hyperventilation provocation did not appear to be very panicogenic in panic disorder patients. In contrast, inhaling 5% CO_2 proved to be more powerful in provoking anxiety in the same subjects. Unfortunately, these experiments suffered from an essential methodological drawback: the hypercapnic condition al-

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ways preceded the hypocapnic condition. As suggested by the authors themselves, this means that a possible order effect cannot be excluded.

Two of our experiments have shown results similar to those reported by Gorman et al. In a recent study we also found that hyperventilation produced only slight anxiety in PD patients (as well as in normals) (Griez et al., 1988), whereas an earlier experiment demonstrated that one vital inhalation of a gas mixture containing 35% CO_2 and 65% O_2 provoked high anxiety (Griez et al., 1987c).

The aim of the present study was to compare the effects of hypercarbia (by means of one vital capacity of 35% CO_2/65% O_2) and hypocarbia (by means of voluntary hyperventilation), in both PD patients and normals, in a random-order cross-over design and strictly standardized circumstances. Our hypothesis was that hypercarbia would cause significantly more anxiety than hypocarbia in panic disorder patients, while in normals no significant difference would be found.

Methods

Subjects

The 12 experimental subjects, four men and eight women, were patients at the Anxiety Clinic of the Academic Psychiatric Hospital. They all met the DSM-III-R criteria for panic disorder (American Psychiatric Association, 1987) and were in good physical condition at the time of the experiment. Their mean age was 33.8 years (range 21–55) and the mean duration of complaints was 4.8 years (range 4 months–9 years).

The 11 control subjects, four men and seven women, with a mean age of 25.5 years (range 18–35), were in good physical condition and had neither current nor past psychiatric problems. All were undergraduate students. No one was familiar with the subject of the experiment.

At the time of the experiment the subjects were free of medication that could possibly influence mental processes. They were asked to refrain from alcohol for 8 h and from food and coffee and/or tea for at least 2 h preceding the test.

Procedure

All subjects underwent a 35% CO_2 challenge as well as a hyperventilation provocation test in a random cross-over design. Half of the subjects hyperventilated first.

Between the two tests there was a period of at least 1 h and at most 1 week.

Both tests were held in the same room with the subject seated in the same chair and surrounded by the same equipment. For both tests the same kind of self-administration mask was used. The subject received similar 'neutral' instructions, which were neither frightening nor reassuring. Both tests included a control condition and the subject had to fill in the same form at similar moments.

CO_2 challenge

The procedure for this test has been described elsewhere (Griez et al., 1987c). Two gases were used: a 35% CO_2/65% O_2 mixture and a compressed air placebo. Both were inhaled through the same self-administration mask (of a modified Entonox apparatus, British Oxygen Company). Both patient and control groups were studied following a double-blind, random-order, cross-over design. Half of the subjects inhaled CO_2 first.

(1) Subjects were told that they were about to inhale two different gases with varying CO_2 concentrations. They were also told that depending on the concentration and on their individual susceptibility it might induce some short-lived physical effects similar to those experienced during exercise.

(2) Instructions were given for the SUDS (Subjective Units of Disturbance Scale; Wolpe, 1973). This scale is designed to measure distress on a continuum ranging from 0 ('no anxiety at all') to 100 ('the most terrifying experience one can imagine').

(3) The subjects were asked to complete a self-rating form to assess the 14 panic criteria listed in the draft of the DSM-III-R, each item ranging from 0 to 4. Subjective fear was quantified in SUDS.

(4) After a deep exhalation, subjects pressed the mask to their faces and took one single vital capacity of the gas mixture. After inhaling, subjects held their breaths for 4 s to enhance alveolar exchanges.

(5) As soon as they were able, subjects reported what they had felt during the test on the form. SUDS were also noted.

(6) After half an hour, steps 3–5 were repeated for the inhalation of the second gas mixture.

Hyperventilation provocation

In the experimental condition, subjects had to breathe through an open mask (hypocapnic hyperpnea, HHP). In the control condition, an open tube, with a length of 78 cm and a diameter of 3.2 cm, was connected to this mask, resulting in an increased dead space (normocapnic hyperpnea, NHP). Following a single-blind, random, cross-over design, each participant underwent both conditions, with an interval of half an hour. Half of the subjects had the HHP condition first.

End-tidal pCO_2 was continuously monitored by means of a Gould Godart Mk III capnograph.

(1) Subjects were told that they were about to undergo two breathing tests, which would be registered in different ways, and that they would have to breathe with a fixed frequency. (The word 'hyperventilation' was avoided.) They were also told that the test might induce some short-lived physical effects.

(2) Instructions were given for the SUDS.

(3) The subjects were asked to complete a self-rating form to assess the 14 panic criteria listed in the draft of the DSM-III-R, each item ranging from 0 to 4. Subjective fear was quantified in SUDS.

(4) In the experimental condition, the subject hyperventilated with a fixed frequency of 30 inhalations per minute. After 1 min the end-tidal pressure (PET) CO_2 was less than 3%; after 2 min it was less than 2.5%. The PET CO_2 was maintained below 2.5% for at least 3 min. An attempt was made to reduce the PET CO_2 to less than 50% of its baseline value.

(5) As soon as they were able, subjects reported what they had felt during the test on the form. SUDS were also noted.

(6) In the control condition, steps 3–5 were repeated, but this time with the tube connected to the mask. The subject performed the same respiration movements as in the hypocapnic condition, now resulting in approximately the same value of PET CO_2 as in baseline breathing.

TABLE 1

CAPNOGRAPHIC PARAMETERS DURING THE HYPERVENTILATION PROVOCATION TEST (PET CO_2 IN vol.%)

	Baseline	Final tube breathing	Final VHV
PD patients ($n = 12$)	4.03 ± 0.636	4.32 ± 0.597	1.93 ± 0.253
Normals ($n = 11$)	4.30 ± 0.458	4.12 ± 0.456	1.90 ± 0.195

Results are expressed as means ± SD.

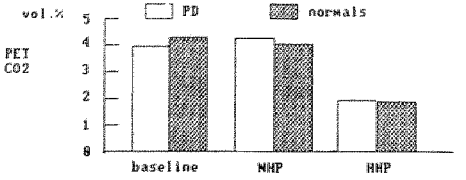

Fig. 1. Mean PET CO_2 (in vol.%) during the hyperventilation provocation test. NHP, normocapnic hyperpnea; HHP, hypocapnic hyperpnea.

Results *

Table 1 and Fig. 1 show the end-tidal CO_2 volume percentages in the hyperventilation test. In neither group were significant differences found between baseline and final tube breathing; both conditions differed significantly from the hypocapnic condition ($P \ll 0.001$, t-test). No differences were found between the two groups in any of the values.

Hyperventilation reduced the PET CO_2 to 47.7% of its original value in the patient group and to 44.2% in the control group.

Anxiety

Table 2 and Fig. 2 show the increase in anxiety (value during the test minus value before the test). The means, standard deviations and levels of significance are shown after the 35% CO_2 inhalation and after the air inhalation. Also shown is the difference between these two. The Table and Figure further illustrate the hypocapnic hyperpnea

* All tests were two-tailed.

TABLE 2

INCREASE IN ANXIETY (IN SUDS)

	Hypercarbia			Hypocarbia		
	CO_2	Air	CO_2 minus air	HHP	NHP	HHP minus NHP
PD patients ($n = 12$)	26.7 ± 24.2 ***	-3.75 ± 14.6 NS	30.4 ± 27.4 ***	9.17 ± 18.3 NS	5.75 ± 17.3 NS	3.42 ± 6.11 NS
Normals ($n = 11$)	4.55 ± 5.52 *	-1.00 ± 3.07 NS	5.55 ± 6.95 *	3.91 ± 4.37 **	-1.27 ± 4.56 NS	5.18 ± 6.95 *

Results are expressed as means $\pm$ SD.

Level of significance: NS, non-significant; *, $P < 0.05$ (t-test, Wilcoxon); **, $P < 0.02$ (t-test)/$P < 0.05$ (Wilcoxon); ***, $P < 0.01$ (t-test, Wilcoxon).

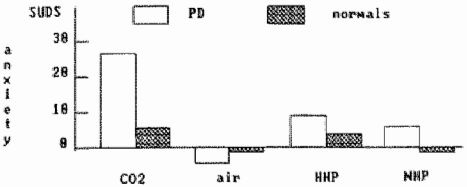

Fig. 2. Mean increase in anxiety (in SUDS).

condition (HHP), the normocapnic hyperpnea condition (NHP) and the difference between these two.

A 3-way analysis of variance (ANOVA) was carried out, the factors being: group (PD vs. normals), condition (hypercarbia vs. hypocarbia) and order of administration (hypercarbia first vs. hypocarbia first). Significance was found for the group main effect ($P < 0.025$), the condition main effect ($P < 0.01$) and the group $\times$ condition interaction ($P < 0.025$). There was neither an order main effect, nor any significant interactions between order $\times$ condition, order $\times$ group or order $\times$ condition $\times$ group.

After this, the data were analyzed in pairs, disregarding differing sequences. The effects of hypercarbia and hypocarbia was significantly different in patients ($P < 0.01$; t-test, Wilcoxon), while in the control group no difference was found. Even when the control conditions were ignored, the difference between the hypercapnic and hypocapnic conditions (CO_2 vs. HHP) was significant

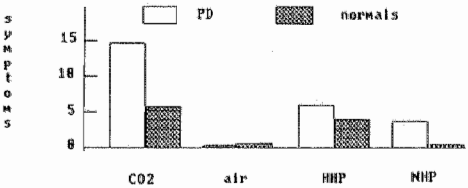

Fig. 3. Mean increase in the number of symptoms.

TABLE 3

INCREASE IN THE NUMBER OF SYMPTOMS

	Hypercarbia			Hypocarbia		
	CO_2	Air	CO_2 minus air	HHP	NHP	HHP minus NHP
PD patients ($n = 12$)	14.8 ± 5.38 ***	0.17 ± 1.90 NS	14.6 ± 5.76 ****	6.17 ± 7.00 **	3.42 ± 4.72 *	2.75 ± 6.72 NS
Normals ($n = 11$)	6.18 ± 4.47 ****	0.55 ± 0.82 NS	5.64 ± 4.97 ***	3.82 ± 2.08 ****	0.36 ± 2.98 NS	3.45 ± 3.93 **

Results are expressed as means $\pm$ SD.

Level of significance: NS, non-significant; *, $P < 0.05$ (t-test)/$P < 0.02$ (Wilcoxon); **, $P < 0.02$ (t-test, Wilcoxon); ***, $P < 0.01$ (t-test, Wilcoxon); ****, $P < 0.001$ (t-test)/$P < 0.01$ (Wilcoxon).

in the patient group ($P < 0.05$; t-test, Wilcoxon), whereas normals showed no difference.

Comparing both groups with respect to the increase in anxiety, it was found that the values were significantly different in two conditions: CO_2 and CO_2 minus air. In both the P value was < 0.01 (t-test, Mann–Whitney U-test). The other values showed no difference.

Symptoms

Table 3 and Fig. 3 show the increase in the number of symptoms (value during the test minus value before the test) in a way similar to that in Table 2 and Fig. 2.

Results were tested by 3-way ANOVA, the factors being: group (PD vs. normals), condition (hypercarbia vs. hypocarbia) and order of administration (hypercarbia first vs. hypocarbia first). Significance was found for the group main effect ($P < 0.025$), the condition main effect ($P < 0.01$) and the group × condition interaction ($P < 0.025$). There was neither an order main effect, nor any significant interactions between order × condition, order × group or order × condition × group.

After this, comparisons were carried out in pairs, disregarding differing sequences. It was found that in the patient group, the difference in symptoms between hypercarbia and hypocarbia was significant (t-test: $P < 0.001$, Wilcoxon: $P < 0.01$). When the control conditions were ignored, significance was found as well ($P < 0.01$; t-test, Wilcoxon). In normals the hypercarbic and hypocarbic conditions were not significantly different.

Comparing both groups with respect to the increase in symptoms, no difference was found in the following conditions: air, HHP, NHP, and HHP minus NHP. In CO_2 and CO_2 minus air, the t-test showed a value of $P < 0.001$ and the Mann–Whitney U-test a P value < 0.01.

No correlations were found between the levels of anxiety in the various conditions and between the level of anxiety and the number of symptoms.

Discussion

In the present study it was found that panic patients experienced significantly more anxiety during the 35% CO_2 challenge test than during hyperventilation provocation. In contrast, the difference between these two tests was not significant in normals. Even when the control conditions (air and NHP, respectively) were ignored, the same pattern was found. Furthermore, CO_2 proved to be more anxiogenic in PD patients than in normals, whereas the slight distress induced by hyperventilation was not significantly different between the two groups. In other words, these results might indicate that panic disorder patients have a specific hypersensitivity to an *increase* in CO_2, while a decrease in CO_2 has very little effect. These findings are in line with earlier studies (Gorman et al., 1984, 1988; Griez et al., 1988).

Does the observation that panic patients are hypersensitive to CO_2 imply that normals are completely insensitive to CO_2? One report has suggested that the anxiety and somatic responses of healthy subjects to 7.5% CO_2 may be similar to the effects of 5% CO_2 in panic disorder patients (Woods et al., 1988). In the present study normals show a small, but significant rise in anxiety after CO_2 inhalation. However, this increase is much smaller than in panic patients. Hence, it can be concluded that normals are not completely insensitive to CO_2, but less sensitive than panic patients.

The results of the present study warrant some further comments. In this trial, two procedures were compared. One was assumed to induce hypercapnia, the other to provoke hypocapnia. It might be suggested that the two tests used in this experiment were not completely comparable. For instance, because the induced hypercarbia was a sudden effect, the increase in pCO_2 happened within seconds, whereas the effect of hyperventilation was rather slow, occurring within 1–2 min. However, it has been demonstrated that inhaling 5% CO_2 for several minutes is very anxiogenic as well (Gorman et al., 1984, 1988). In addition, although the hyperventilation provocation resulted in a slower change in pCO_2 than one inhalation of 35% CO_2, the pCO_2 was reduced for at least 3 min, whereas the rise in pCO_2 merely lasted for some seconds.

There might be another argument supporting the suggestion that the two tests were not completely comparable. The fact that the increase in symptoms in panic patients during the 35% CO_2 inhalation was significantly greater than during

hyperventilation might suggest that the absolute magnitude of the two disturbances was not equal. However, there are several arguments in favor of an approximately equal magnitude of both stimuli. First, in normals, the rise in symptoms was not significantly different in the two conditions. A second argument is based on the change in blood pH in the two conditions. The 35% CO_2 challenge test results in a decrease in pH of about 0.3 (Griez et al., 1987b). Hyperventilation which causes a decrease in pCO_2 of more than 50%, as in this experiment, results in a rise in pH of approximately 0.25 (Stortenbeek, 1979).

Although the change in pH seems to be slightly greater during hypercarbia, it must be noted that in the hypercarbic condition the duration of maximal pH change is very short, while in the hyperventilation provocation test the change in pH lasts for at least 3 min. Hence, it seems reasonable to assume that the absolute pH change in the cerebral fluids is approximately the same or might even be smaller during the 35% CO_2 inhalation.

On the basis of these considerations one might reasonably conclude that the two experimental conditions were comparable. If this is, in fact, the case, how can one explain the finding that in PD patients both SUDS *and* symptoms seem to increase during *hyper*carbia? One explanation could be that a directly CO_2-induced rise in anxiety causes neurovegetative stimulation, resulting in various symptoms. More anxiety would result in more symptoms. Another possibility might be that PD patients react to a situation of hypercarbia with more symptoms, in a way that is yet unclear. *These symptoms might indirectly lead to subjective* anxiety according to the principle of 'fear of symptoms' of 'fear of fear' (Van den Hout et al., 1987; Ley, 1987). Both possibilities suggest a specific hypersensitivity to CO_2, with or without the mediation of symptoms.

Several theories can be – and have been – postulated in order to explain this hypersensitivity to CO_2. It might be suggested that the panicogenic influence of CO_2 is the result of its stimulating effect on the locus ceruleus (Elam et al., 1981). Another hypothesis is that CO_2 might influence the serotonergic system (Lingjaerde, 1985). A third possibility could be a hypersensitivity of the central chemoreceptors to CO_2, a postulation which is supported by an experiment demonstrating the existence of an increased sensitivity to CO_2, as measured by ventilatory responses (Lousberg et al., 1988). A general stimulation of neuronal activity as a result of a rise in pCO_2 might be a fourth explanation (Griez et al., 1987c).

The present experiment gives no indication in favor of one or more of these theories. Additional research on various experimental disturbances of the acid–base status of the blood, for example, are warranted.

In conclusion, it seems that in susceptible patients hypercarbia is more anxiogenic than hypocarbia. This suggests a specific hypersensitivity to CO_2 in panic disorder patients.

Acknowledgements

Thanks are expressed to Mrs. A. Demmers, research assistant, for her indispensable assistance and to Mr. R. van Diest for his statistical aid.

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2.2.3 An analysis of panic symptoms during hypercarbia compared to hypocarbia in patients with panic attacks

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Journal of Affective disorders, in press

Journal of Affective Disorders, 00 (1991) JAD00847

ADONIS 01650327•

JAD 00847

An analysis of panic symptoms during hypercarbia compared to hypocarbia in patients with panic attacks

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(Received 16 April 1991)
(Revision received 26 July 1991)
(Accepted 18 August 1991)

Summary

Twenty panic disorder patients underwent a 35% CO_2 challenge test and a hyperventilation provocation test. CO_2-induced anxiety proved to correlate sinificantly with respiratory symptoms. These symptoms appeared to be considerably more severe during CO_2 inhalation than during the hyperventilation provocation test, which induced no significant anxiety.

Key words: Panic disorder; Carbon dioxide; Hyperventilation provocation; Respiration

Introduction

In the last decade carbon dioxide (CO_2) inhalation has become a well established experimental method for panic provocation in panic disorder (PD) subjects. The most extensively studied procedures include prolonged administration of 5% CO_2 (Gorman et al., 1984, 1988; Woods et al., 1988) and one vital capacity inhalation of 35% CO_2 (Griez et al., 1987a). With both methods PD patients have been demonstrated to be highly vulnerable to experimental hypercarbia, whereas healthy control subjects are hardly affected. There are strong indications that the CO_2 model is specific for PD subjects, as the 35% CO_2 challenge technique has been shown to differentiate between PD and obsessive-compulsive disorder (OCD) (Griez et al., 1990a). Baseline arousal was suggested to play a role in CO_2-induced anxiety; however, it has been demonstrated that CO_2-provoked panic cannot merely be attributed to increased baseline anxiety (Griez et al., 1990b).

CO_2 inhalation can produce various physical symptoms, most of which are neurovegetative in nature. Some of these autonomic changes may give indications about the mechanisms behind CO_2-induced panic. Therefore, it seemed of interest to identify which specific panic symptoms

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correlated best with subjective anxiety during CO_2-induced panic.

Like CO_2 inhalation, hyperventilation provocation (HVP) has also been found to produce various somatic symptoms resembling those of panic. In the past it had been argued that hypocarbia might play an important role in anxiety induction in naturally occurring panic and/or hyperventilation (Lum, 1975; Beumer and Hardonk, 1980; Hibbert, 1984; Ley, 1985; Folgering, 1986). However, recent reports have demonstrated that hyperventilation provocation is definitely less panicogenic than CO_2 inhalation in PD patients (Gorman et al., 1984, 1988; Zandbergen et al., 1990). Since both HVP and CO_2 inhalation are effective in provoking panic-like symptoms, but clearly differ with respect to the induction of subjective anxiety, it seemed of interest to know which symptoms, or cluster of symptoms, differed between experimental hypercarbia and hypocarbia. These symptoms might be specifically related to the subjective anxiety of panic.

The present study dealt with both above-mentioned questions by investigating symptom profiles during the 35% CO_2 challenge and hyperventilation provocation in PD patients, in order to identify which specific panic symptoms are of major importance to CO_2-induced subjective anxiety. The data were partially taken from two previous studies (Griez et al., 1988; Zandbergen et al., 1990), which had been designed for a different purpose, namely to explore the anxiogenic capacity of experimental hypercarbia and/or hypocarbia in PD as compared to healthy controls.

Methods

Subjects

The 20 experimental subjects, eight men and 12 women, were outpatients at the Anxiety Clinic of the Academic Mental Hospital Vijverdal. They all met DSM-IIIR criteria for panic disorder with or without avoidance (American Psychiatric Association, 1987) and their mean age was 34.9 years (range 21–55). At the time of the experiment they were not undergoing psychiatric treatment, had been free of psychotropic medication for at least 1 week, and were in good physical condition. Subjects had to refrain from alcohol for at least 8 h and from tea and coffee for at least 2 h preceding the tests.

The experimental data of 12 of the 20 subjects were taken from an earlier study (Zandbergen et al., 1990), as were the hyperventilation data of the other eight subjects (Griez et al., 1988), who had also undergone a 35% CO_2 challenge.

Procedure

The procedures of the 35% CO_2 challenge technique and the hyperventilation provocation test used in the present study have been described in detail elsewhere (Griez et al., 1988, 1990a; Zandbergen et al., 1990). Each subject underwent a 35% CO_2 challenge and a hyperventilation provocation test in a random crossover design.

In the CO_2 challenge test subjects inhaled one vital capacity of two different gas mixtures, one consisting of 35% CO_2 and 65% O_2, and the other consisting of air.

In the HVP test subjects hyperventilated for at least 3 min through an open mask, resulting in a reduction of end-tidal pCO_2 ($PETCO_2$) of at least 50% (hypocapnic hyperpnea, HHP). In the control condition (normocapnic hyperpnea, NHP) the same procedure was repeated with an open tube connected to the mask, resulting in approximately the same value of $PETCO_2$ as in baseline breathing.

Assessments

Immediately before and after each test, the subjects completed a self-rating form to assess 14 panic criteria, according to the draft of DSM-IIIR (Tables 1 and 2), each item ranging in value from 0 to 4. This yielded a total symptom score (range 0–56). In addition, they were asked to express their subjective feeling of anxiety on a scale ranging from 0 (no anxiety at all) to 100 (the worst imaginable experience).

During the hyperventilation tests (HHP and NHP), the end-tidal pCO_2 was continuously monitored by means of a Gould Godart Mk III capnograph.

Data analysis

For the 35% CO_2 challenge test, a net score for subjective anxiety was calculated with the

following formula: (value after CO_2 minus value before CO_2 minus (value after air minus value before air). A similar formula was used for calculation of net scores for symptoms.

Net scores for the hyperventilation provocation test were calculated using the formula: (value during HHP minus value before HHP) minus (value during NHP minus value before NHP).

For the CO_2 and the HVP conditions separately, the correlation coefficients between net subjective anxiety on the one hand and the net scores of the total number of symptoms and each individual symptom on the other hand were calculated.

The net subjective anxiety scores in both conditions were compared using parametric and non-parametric tests for related samples. The net total number of symptoms was analyzed in a similar way.

For all symptoms together the net scores of CO_2 and the hyperventilation test were compared using MANOVA. If a significant difference was found, pairwise comparisons were performed (parametric and non-parametric).

Results

Table 1 shows the correlation coefficients between the net increase in anxiety and the panic symptoms which subjects experienced during the 35% CO_2 challenge. It also shows correlation coefficients for the hyperventilation condition.

Table 2 shows the net increases in subjective anxiety, the total number of symptoms and the 14 separate symptoms during the 35% CO_2 challenge and the hyperventilation provocation test. A significant difference was found between experimental hypercarbia and hypocarbia with respect to the increase in subjective anxiety and the total number of symptoms.

Analysis by means of MANOVA revealed a significant difference for all DSM-IIIR symptoms

TABLE 1

CORRELATION COEFFICIENTS BETWEEN INDUCED PANIC SYMPTOMS AND EXPERIENCED ANXIETY DURING 35% CO_2 AND HVP

	Correlation of induced panic symptoms with experienced anxiety during CO_2	Correlation of induced panic symptoms with experienced anxiety during HVP
Total symptoms	0.460 ($P = 0.041$)	0.249 (NS)
Symptoms		
1. shortness of breath or smothering sensations	0.536 ($P = 0.015$)	0.539 ($P = 0.014$)
2. choking	0.521 ($P = 0.019$)	0.222 (NS)
3. palpitations or accelerated heart beat	0.352 (NS)	0.407 ($P = 0.075$) (= trend)
4. chest pain or discomfort	0.088 (NS)	−0.005 (NS)
5 sweating	0.167 (NS)	0.103 (NS)
6 faintness	0.082 (NS)	0.205(NS)
7. dizziness, lightheadedness or unsteady feelings	0.166 (NS)	−0.112 (NS)
8. nausea or abdominal distress	−0.012 (NS)	0.101 (NS)
9. depersonalization or derealization	0.394 ($p = 0.085$) (= trend)	−0.075 (NS)
10. numbness or tingling sensations	0.116 (NS)	−0.072 (NS)
11. flushes or chills	−0.214 (NS)	0.442 ($P = 0.051$) (= trend)
12. trembling or shaking	0.039 (NS)	−0.022 (NS)
13. fear of dying	0.266 (NS)	0.135 (NS)
14. fear of going crazy or of doing something uncontrolled	0.388 ($P = 0.091$) (= trend)	0.171 (Ns)

TABLE 2

DIFFERENCE BETWEEN THE 35% CO_2 CHALLENGE AND HVP

	Net value during CO_2	Net value during HVP	Difference between CO_2 and HVP	
			t-test	Wilcoxon
Subjective anxiety	30.0 ±28.7	4.5 ±7.0	$P = 0.001$	$P = 0.0016$
Total symptoms	11.7 ± 6.5	4.9 ±6.5	$P = 0.008$	$P = 0.0052$
Symptoms				
1. shortness of breath or smothering sensations	1.60 ± 0.99	0.40 ± 0.60	$P = 0.000$	$P = 0.0011$
2. choking	1.20 ± 1.06	0.40 ± 1.05	$P = 0.032$	$P = 0.0495$
3. palpitations or accelerated heart beat	1.05 ± 0.89	0.35 ± 0.88	$P = 0.059$ (trend)	$P = 0.0597$ (trend)
4. chest pain or discomfort	0.40 ± 1.47	0.20 ± 1.40	NS	NS
5. sweating	0.65 ± 0.99	0.25 ± 0.91	NS	NS
6. faintness	1.10 ± 1.12	0.55 ± 1.70	NS	NS
7. dizziness, lightheadedness or unsteady feelings	1.45 ± 1.05	0.50 ± 1.28	$P = 0.002$	$P = 0.0052$
8. nausea or abdominal distress	0.75 ± 0.79	−0.10 ± 1.33	$P = 0.007$	$P = 0.0146$
9. depersonalization or derealization	0.75 ± 1.07	0.50 ± 1.00	NS	NS
10. numbness or tingling sensations	0.65 ± 1.50	0.80 ± 1.15	NS	NS
11. flushes or chills	0.90 ± 1.07	0.05 ± 0.69	$P = 0.009$	$P = 0.0087$
12. trembling or shaking	0.65 ± 0.93	0.55 ± 1.19	NS	NS
13. fear of dying	0.50 ± 1.00	0.25 ± 0.64	NS	NS
14. fear of going crazy or of doing something uncontrolled	0.50 ± 0.95	0.30 ± 0.57	NS	NS

together ($S = 1$, $M = 6$, $N = 2$; Pillais, Hotellings, Wilks; $P = 0.045$). Individual symptoms during hypercarbia and hypocarbia were compared using t-tests ($df = 19$) and Wilcoxon tests, as shown in Table 2.

No significant order effects were found.

Discussion

In the present study it was found that during CO_2 inhalation 'shortness of breath' and 'choking' correlated significantly with subjective anxiety (Table 1). During hyperventilation provocation, the anxiety induced, although weak, correlated significantly with 'shortness of breath'. In other words, in both experimental conditions anxiety correlated best with respiratory symptoms.

During CO_2 inhalation, trends for a significant correlation with subjective anxiety were found for 'depersonalization of derealization' and 'fear of going crazy or of doing something uncontrolled'. For the latter symptom this is obviously due to auto-correlation. During HVP, trends for a significant correlation with subjective anxiety were found for 'palpitations or accelerated heart beat' and 'flushes or chills'; but as mentioned above, HVP is a very weak anxiogenic. Moreover, since multiple correlations were performed, any conclusions concerning these findings of trends seem rather presumptious.

Concerning the comparison of the 35% CO_2 challenge and HVP it is noteworthy that the absolute (but opposite) pH changes are approximately equal in the two conditions. One vital capacity inhalation of 35% CO_2 results in a pH decrease of about 0.3 (Griez et al., 1987b), while hyperventilation as described above results in a pH rise of approximately 0.25 (Stortenbeek, 1979). However, the rate at which these pH changes develop is much higher in the hypercarbic than in the hypocarbic condition. The 35% CO_2 challenge causes a decrease in pH within seconds, whereas during HVP the pH increase occurs within 1–2 min, a rate at least 10 times slower than during 35% CO_2 inhalation. It was found that a rapid increase in pCO_2 results in a greater increase in panic symptoms and subjective anxiety than a relatively slow decrease in pCO_2. Both the

direction of pCO_2 (and pH) changes and the rate at which these changes develop could be an important factor in the induced symptoms and anxiety.

When the symptom profiles of these hypercarbic and hypocarbic conditions were compared, it was found that the effect of 35% CO_2 inhalation was greater than HVP for five symptoms (Table 2). Both respiratory symptoms ('shortness of breath' and 'choking') were included in these 5. The other three symptoms ('dizziness', 'nausea' and 'hot or cold flashes') were not related to CO_2-induced anxiety, and therefore are probably of minor importance to the anxiety provoked.

Regarding these findings, it could be argued that the rapid increase in pCO_2 and decrease in pH as a consequence of a 35% CO_2 inhalation result in an acute stimulus to respiration and the appearance of respiratory symptoms, which in turn induce high anxiety by the principle of 'fear of symptoms' (Van den Hout et al., 1987) or 'catastrophic misinterpretation' (Clark, 1986). As HVP induces less severe respiratory symptoms, this cognitive mechanism would explain the difference between the hypercarbic and hypocarbic conditions. Furthermore, since CO_2 directly affects the repiratory system, it would not seem surprising that mainly respiratory symptoms are involved. On the other hand, symptoms such as palpitations, faintness and dizziness, which are well known signs accompanying experimental as well as real-life panic, also clearly occurred during the 35% CO_2 challenge to a degree comparable to that of respiratory symptoms. According to cognitive theory these symptoms would be expected to be anxiogenic in PD (Van den Hout et al., 1987). However, in the present study palpitations, faintness and dizziness were hardly related to CO_2-induced anxiety. This could suggest a specific role of respiratory symptoms in PD, although this speculation should be confirmed, for instance by means of studies which compare anxiety and symptom profiles during CO_2 inhalation with challenges that have a less direct effect on the occurrence of respiratory symptoms.

The apparent importance of respiratory symptoms in CO_2-provoked panic seems of particular interest when these results are combined with those of recent research on co-morbidity of PD and diseases affecting the respiratory system. In a previous study we found that PD patients had a higher lifetime prevalence of respiratory diseases than either obsessive-compulsive disorder patients or eating disorder (Zandbergen et al., 1991). Karajgi et al. (1990) found a higher prevalence of PD in a group of patients with chronic obstructive pulmonary disease than in the general population. Taken together, these finding suggest that respiratory symptoms might play an important role in real-life panic in a substantial subgroup of PD patients.

Should this close association of panic and respiration be confirmed, it could point to a strong functional relationship between brain structures responsible for respiration and those involved in panic. The locus coeruleus, for example, has been suggested to be involved in panic (Gorman et al., 1984) and has been demonstrated to be stimulated by CO_2 (Elam et al., 1981). Nuclei in the dorsal raphe, which produce serotonin, may play a role as well (Lingjaerde, 1985; Pols and Griez, 1988; Kahn et al., 1988). Both structures have been demonstrated to influence respiration (Eldridge and Millhorn, 1981; Mueller et al., 1982).

A third possibility connecting panic and respiratory symptoms might be the existence of hypersensitive central chemoreceptors in PD, as has been suggested by a recent study (Lousberg et al., 1988).

In conclusion, the results of the present study indicate that respiratory symptoms are of major importance in CO_2-induced panic. Although various other panic symptoms such as palpitations, faintness and dizziness were also clearly provoked by 35% CO_2, they did not significantly correlate with the anxiety PD subjects experienced.

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2.3

FURTHER STUDIES ON RESPIRATORY DISREGULATION

2.3.1 Breath-holding in panic disorder

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Comprehensive Psychiatry, in press

ABSTRACT

In earlier studies it was found that exogenous carbon dioxide administration provoked high anxiety in panic disorder patients, whereas healthy normals and patients suffering from other anxiety disorders were hardly affected. Breath-holding seems a simple method to induce endogenous CO2 accumulation. Fourteen panic disorder patients, fourteen patients suffering from other anxiety disorders and fourteen healthy controls were asked to hold their breath as long as possible. Apnea times appeared to be higher in the normal control group than in the other two groups. A trend for a difference was found between the PD subjects and other anxiety patients with a one tailed t-test, the PD patients having slightly lower values. No difference was found with respect to increase in anxiety during breath-holding, while the ratio of apnea times before and after hyperventilation showed no difference either.

INTRODUCTION

Various methods of carbondioxide (CO2) administration have been described for provoking anxiety in panic disorder (PD) patients. Prolonged administration of a gas mixture containing 5% CO2 has been demonstrated to induce panic in PD patients, whereas healthy controls seem to be hardly affected (1)(2)(3). One vital capacity inhalation of a gas mixture with 35% CO2 also rapidly triggers anxiety in PD patients, in contrast to normals, who experience only slight increase in anxiety (4). Furthermore, the 35% CO2 challenge technique differentiates between PD and obsessive compulsive disorder (OCD) (5), while 35% CO2 provoked panic attacks are not merely a consequence of increased base-line anxiety (6).

These models concern exogenous administration of CO2. A simple and very natural method of inducing endogenous pCO2 increase may be breath-holding. This technique has been used in some disorders other than PD, in which cases it was intended to be a test for autonomic failure (7). Bass has reported that patients with chest pain and normal ECG and with a positive hyperventilation provocation test demonstrated a shorter breath- holding time than normal control subjects (8). In patients with neurocirculatory dystonia (NCD), a syndrome possibly related to PD, Mäntisaari (9) used an extended version of a breath-holding test. This version had originally been developed by Friedman as a test to support the diagnosis of functional cardiovascular disease (10)(11). Subjects were asked to hold their breath as long as possible. Immediately after a 45-second period of hyperventilation breath-holding was repeated and the ratio of the these two breath holding times, the "hyperventilation index" (HI) was calculated. Mäntisaari found that the ability to hold ones breath after a deep inspiration of air was similar in 30 male NCD subjects and 30 male normal controls, but the HI tended to be higher in normals than in NCD patients (9).

The breath-holding test might be of interest in PD for two reasons. Firstly, it seems a method to test a vulnerability to endogenous pCO2 increase. Secondly, PD patients show signs of autonomic dysfunction (12)(13), even after succesful psychological treatment (14).

In the present study we decided to use the test as described by Mäntisaari (9). Three groups of subjects were selected, one consisting of PD patients, another of patients

suffering from other anxiety disorders, and finally a group of healthy controls. Since CO2 inhalation appears to differentiate between PD on the one hand and other anxiety disorders and normal controls on the other hand, our hypothesis was that the breath-holding time would be smaller in PD patients than in other anxiety disorder subjects and normal controls. Moreover, it was expected that the HI would be smaller in PD patients than in either other anxiety disorder patients and healthy controls. The main intention of the present study was to explore whether breath-holding might serve as a simple test supporting the diagnosis of PD in patients with anxiety disorders. Therefore we decided to choose a design which was practical, uncomplicated and easy to perform.

METHODS

Subjects

Three groups of subjects participated in this study. The first group consisted of 14 PD patients with a mean age of 33.4 (s.d. 7.24) years. The second group consisted of 14 patients suffering from another anxiety disorder with a mean age of 32.4 (s.d. 10.3) years. Nine of them were suffering from obsessive-compulsive disorder, 3 from generalized anxiety disorder, and 2 from social phobia. The patients had been referred to the local Academic Anxiety Center Vijverdal and had been diagnosed by experienced clinicians using the DSM-III-R critera (15). The third group consisted of 14 healthy control subject with neither past nor current psychiatric problems and with a mean age of 32.5 (s.d. 7.77) years.
Each group consisted of 7 men and 7 women and all subjects were in good physical health and not under current psychiatric treatment. They had been free of medication that could possibly influence mental processes for at least 2 weeks, except for incidental use of low dosages of benzodiazepines (BZ). In the PD group 10 subjects used no BZ, 3 patients used a daily dose equivalent to $\leq$ 5 mg diazepam/day, while one PD patient used BZ equivalent to $\leq$ 15 mg diazepam/day. In the other anxiety disorder group 10 subjects used no BZ, 2 patients used BZ equivalent to $\leq$ 5 mg diazepam, and 2 subjects equivalent to $\leq$ 10 mg diazepam. None of the normal controls used BZ.
Subjects were asked to refrain from alcohol for at least the last 8 hours and from coffee, tea, or food for at least the last 2 hours preceding the test.

Procedure

After the explanation of the procedure (in which the word "hyperventilation" was avoided) subjects were asked to complete a self-rating form to assess severity of the 13 panic symptoms listed in the DSM-III-R, each item ranging from 0 to 4. A total symptom score was calculated by adding up the scores of the 13 items. In addition, subjective anxiety was quantified on a line of 100 mm, ranging from "no anxiety at all" to "the most terrifying experience one can imagine". Hereafter subjects were asked to take a deep breath of a gas mixture containing 50% O2 and 50% N2, using a self-administration mask (Entonox^R, British Oxygen Company, Ltd.), and to hold it as long as possible. This O2-enriched air was used in order to exclude possible limitations in breath-holding capacity due to hypoxia. The duration of apnea was measured, starting

from the beginning of the deep breath. After breath-holding, subjects again completed the panic symptom list and pointed out their level of subjective anxiety, now referring to the period of breath-holding.
After 3 minutes this procedure was repeated, but before holding their breath subjects had to hyperventilate for about 1 minute. Before and during hyperventilation the end-tidal CO2 pressure (PET CO2) was measured with a Gould Godart Mk III capnograph. During hyperventilation an attempt was made to reduce the PET CO2 to less than 50% of its baseline value. Subjective anxiety and panic symptoms were measured before hyperventilation and after breath-holding, the latter referring to the period of apnea.
For each breath-holding period the increase of subjective anxiety and panic symptoms was calculated (value during apnea minus value before apnea). The hyperventilation index (HI) was assessed by calculating the ratio of breath-holding time after and before hyperventilation.

RESULTS

Table 1 shows various parameters relevant to the first part of the test, i.e. before hyperventilation.

Table 1. Means and standard deviations of various parameters before hyperventilation.

	PD (n=14) 7 men 7 women	other (n=14) anxiety 7 men 7 women	normals (n=14) 7 men 7 women
age (years)	33.4 (7.24)	32.4 (10.3)	32.5 (7.77)
first breath holding time (seconds)	34.4 (15.2)	48.6 (30.0)	74.4 (38.1)
baseline anxiety	13.8 (12.19)	17.4 (21.88)	4.2 (5.74)
baseline symptoms	3.43 (6.95)	2.71 (2.67)	0.29 (0.83)
increase in anxiety	7.1 (10.38)	2.9 (10.50)	3.1 (7.49)
increase in symptoms	1.07 (5.36)	1.14 (3.68)	4.36 (4.24)

There was no significant difference in age and gender distribution between the 3 groups. Analysis by means of one-way ANOVA revealed a significant difference in breath-holding time ($F=6.673$, $df=2,39$, $p=0.003$). Corresponding two-tailed t-tests showed a significant difference between PD and normals ($t=3.65$, $df=26$, $p=0.001$) and a strong trend for a difference between other anxiety disorders and normals ($t=1.99$, $df=26$,

p=0.057), while there was no difference between PD and other anxiety disorders (t=1.58, df=26, p=0.126). Using a one-tailed t-test, a trend for a difference was found PD and other anxiety subjects (p=0.063), the PD subjects having slightly lower breath-holding times.

Apnea times were also analyzed by non-parametric tests. The three groups differed significantly (Kruskal-Wallis, p=0.0048). Healthy controls had significantly higher breath-holding times than both PD patients (Mann-Whitney U test, p=0.0012) and other anxiety disorder subjects (Mann-Whitney U test, p=0.0429), whereas the PD and other anxiety disorder group showed no significant difference (Mann-Whitney U test, p=0.2693).
Using one-way ANOVA, no differences were found with respect to baseline number of panic symptoms (F=2.033, df=2,39, p=0.145), and increase in anxiety (F=0.847, df=2,39, p=0.436). Trends for a difference were found for baseline anxiety (F=2.937, df=3,39, p=0.065) and increase in number of symptoms (F=2.460, df=2,39, p=0.099).
Pearson correlation coefficients (cc.) between breath-holding time and the following parameters were calculated: baseline anxiety (cc. = -0.2929, p=0.030), the baseline number of symptoms (cc. = -0.1105, p=0.243), the increase in anxiety (cc. = -0.1288, p=0.208) and the increase in symptoms (cc. = 0.4303, p=0.002).
Of the 42 subjects, 35 succeeded in decreasing their pCO2 to 50% or less of the baseline value (table 2). These subjects were included in a further analysis of breath-holding times after hyperventilation and HI's. Although apnea times after hyperventilation provocation showed a highly significant difference (F=10.659, df=2,32, p<0.001), the HI's were not significantly different (F=1.642, df=2,34, p=0.210).

Table 2. Means and standard deviations of various parameters after hyperventilation resulting in pCO2 less than, or equal to 50% of the baseline value.

	PD (n=11) 6 men 5 women	other (n=11) anxiety 5 men 6 women	normals (n=13) 7 men 6 women
second breath holding time (seconds)	61.3 (46.90)	75.7 (64.25)	159.2 (57.32)
hyperventilation index (HI)	1.69 (0.587)	1.63 (1.154)	2.20 (0.710)

DISCUSSION

In the present study PD patients and normal controls showed a significant difference in breath-holding times. This difference in apnea times could not be attributed to

differences in sex distribution or age, since the groups were almost perfectly matched with respect to these factors. It was found that PD patients had significantly lower apnea times than normals. However, patients suffering from other anxiety disorder also tended to have lower breath-holding times than healthy controls. No significant difference was found between the PD and other anxiety disorder group (two-tailed t-test; Mann Whitney U), although there was a trend towards lower apnea times in PD than in other anxiety using a one tailed t-test.
The increase in anxiety during breath-holding, and the "hyperventilation index" (HI) showed no difference between the 3 groups.
In other words, it seems that neither breath-holding nor the HI can serve as simple tests supporting the diagnosis of PD in patients with anxiety disorders.
However, from a theoretical point of view, the results deserve further attention. To our knowledge, this is the first study reporting different breath-holding times between PD subjects and healthy controls. Since other anxiety disorder subjects also had lower apnea times than normals, and both anxiety groups tended to have higher baseline anxiety than healthy controls, it seems obvious that anxiety and/or suffering from an anxiety disorder have contributed to decreasing breath-holding capacity. However, a trend for a difference in apnea times with a one-tailed t-test was found between PD and other anxiety subjects, PD patients having slightly lower breath-holding times. As these findings were found in rather small groups, significant differences might have been found in a larger sample size. If baseline anxiety has had an effect of decreasing breath-holding times, this has been the strongest in the other anxiety group, since this group tended to experience highest baseline anxiety. In other words, if the PD and other anxiety group had had the same level of baseline anxiety, the difference between these 2 groups would have become greater, and possibly have reached significance.
The expectation of a decreased breath-holding capacity in PD was based on our previous findings that the 35% CO2 challenges provoked more anxiety in PD subjects than in patients suffering from other anxiety disorders (5)(6). The increase in subjective anxiety during breath-holding in the present study was however small (table 1) and not significantly different between the 3 groups. Probably, the CO2 accumulation, due to breath-holding, was too small to provoke panic. It is likely that the subjects started breathing again well before the point of panic was reached. Therefore, it could be argued that the breath-holding test is more comparable to assessment of ventilatory response to CO2 (RCO2) than to panic provocation by means of CO2. Data on RCO2, which is assumed to measure chemosensitivity to CO2, unfortunately show conflicting results. Some studies find higher RCO2 values in PD than in normals (16)(17), whereas others do not show differences between PD and healthy subjects (18)(19)(20).
Comparison of breath-holding times with RCO2 implicitly assumes that the endogenous CO2 accumulation, as a consequence of breath-holding, is similar in each experimental group. However, many PD subjects seem to be in a continuous state of hyperarousal, as is reflected in, for instance, a raised resting heart rate and blood pressure (12)(13). Therefore, it could be argued that PD patients have a higher basal metabolism than normal controls, resulting in a greater CO2 production in PD than in normals. On the other hand, if higher endogenous CO2 production was the only mechanism to explain the difference between PD patients and normals, it would seem logical that the increase in physical symptoms during breath-holding would be approximately equal in either group. Subjects with higher endogenous CO2 production would merely start breathing

earlier because they would reach a certain level of symptoms, forcing them to end apnea, earlier. However, in the present study PD subjects tended to experience less symptoms than normals and there was a positive correlation between breath-holding times and increase in somatic symptoms. Obviously, the longer subjects held their breath, the more symptoms they experienced. In other words, it seems that the reason why PD patients started breathing earlier than others, can not be attributed to a more rapid development of physical symptoms.
An alternative explanation for the present findings may be given by the concept of "fear of symptoms" (21) or "catastrophic misinterpretation" (22). According to these theories various physical symptoms act as danger signals in PD subjects. Some of these symptoms, as for instance dyspnea, are provoked by breath-holding. In order to avoid experiencing these symptoms PD patients would start breathing again as soon as these fearful physical symptoms begin to appear. The finding that PD patients tended to have a smaller increase in physical symptoms than normal controls in the present study would support these cognitive mechanisms, although, on the other hand, other anxiety patients experienced a similar rise in symptoms as PD subjects.
Many factors may influence breath-holding, most of which could be controlled for in the present study. As already mentioned, the groups were almost perfectly matched with respect to sex distribution and age. The possible influence of pO2 was controlled for by adding extra O2 in the air that subjects inhaled before holding breath.
It could be argued that the incidental use of benzodiazepines (BZ) may also have affected the present results, as it is known that BZ may have an effect on both respiration and CO2 sensitivity (23)(24). Only 4 subjects in each anxiety group used BZ, most of them in low dosages. If this BZ use has influenced the present results at all, it may have blurred the already clear distinction between normals on the one hand, and both anxiety groups on the other hand. Since BZ intake was approximately equal in both patient groups, it seems unlikely that it affected the difference in apnea times between PD and other anxiety subjects.
In conclusion, PD patients, as well as subjects suffering from other anxiety disorders, were found to have shorter breath-holding times than normals. The results with respect to PD versus other anxiety patients are less clear, and warrants further investigation.

ACKNOWLEGDEMENTS

Thanks are expressed to Catrien de Loof, PhD., and Jos Jurgens, research assistent, for their indispensible assistance in the diagnostic procedure and in gathering the data.

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2.3.2 Ventilatory response to CO2 in Panic Disorder

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Psychiatry Research, 39/1:13-19, 1991

ABSTRACT

The ventilatory response to inhalation of carbon dioxide was measured in 15 panic disorder patients, 15 obsessive-compulsive disorder patients and 15 healthy control subjects, using the Read rebreathing technique. No significant differences in ventilatory response were found between the three groups. The tidal volume and frequency components of the ventilatory response showed no difference between the groups either. The hypothetical pCO2 value corresponding with zero ventilation was significantly lower in the PD patients than in normal controls.

INTRODUCTION

In the last decade it has become well established that panic disorder (PD) patients are highly vulnerable to inhalation of carbon dioxide (CO2). Prolonged adminstration of 5% CO2 (Gorman et al., 1984, 1988; Woods et al., 1988), as well as one vital capacity inhalation of 35% CO2 (Griez et al., 1987) appear to induce anxiety in PD patients, whereas healthy controls are hardly affected. Moreover, it has been demonstrated that the 35% CO2 challenge technique distinguishes between PD and obsessive- compulsive disorder (OCD) patients (Griez et al., 1990a), and that panic provocation is not merely a result of increased baseline anxiety (Griez et al., 1990b). These observations offer strong evidence that only PD patients are hypersensitive to CO2 inhalation.

One possible explanation for this behavioral vulnerability to CO2 is that subjects with PD have hypersensitive CO2 chemoreceptors (Carr & Sheehan, 1984; Gorman et al., 1988). The ventilatory response to CO2 inhalation (RCO2) may be used as a parameter of central chemosensitivity to CO2; this is done by measuring the respiratory minute volume at different concentrations of inhaled CO2. In a previous study, using Read's rebreathing technique (Read, 1967), we found that the RCO2 was significantly higher in 19 PD patients than in 14 healthy controls (Lousberg et al., 1988). Using the steady-state canopy procedure, Papp et al. (1989) reported a greater RCO2 in 7 male PD patients than in 5 normal male control subjects. On the other hand, various studies, using Read's rebreathing technique, found similar responses in PD subjects and in normals (Woods et al., 1986; Pain et al., 1988). Pain et al. (1988) did however find a lower sensitivity with reference to the tidal volume component in PD subjects than in normal controls, and a higher sensitivity with reference to the respiratory frequency component in the PD group than in the control group.

If hypersensitive chemoreceptors were to be responsible for the difference in CO2-induced anxiety between PD and OCD, it would be expected that measuring ventilatory response to CO2 would also distinguish between PD and OCD.

With this hypothesis in mind the present study was conducted.

The Read rebreathing technique (Read, 1967) was used to determine CO2 sensitivity, since it is a fast and simple method.

METHODS

Subjects

15 PD patients and 15 OCD patients participated in the study. All patients had been referred to the local Academic Anxiety Center and were diagnosed by experienced clinicians, using DSM-III-R criteria (APA, 1987). At the time of the study they were not under psychiatric treatment.
A second control group, consisting of 15 healthy subjects, was also included. They had neither past nor current psychiatric problems.
All subjects were in good physical condition and had been free of medication for at least 2 weeks. They were asked to refrain from alcohol during the last 8 hours, and from coffee, tea or food during at least the last 2 hours preceding the experiment.
Table 1 shows sex distribution, age, height, weight, body surface, forced vital capacity (FVC), and forced expiratory volume (FEV1) of the 3 groups.

Procedure

Beforehand, subjects were told that the rebreathing test might induce some slight, but harmless, physical sensations, which would disappear quickly upon completion of the test. They were also told that they could stop the test at any time.
Forced vital capacity (FVC) and forced expiratory volume (FEV1) were assessed using a 10 liter spirometer (Gould Pulmograph). After these pulmonary tests, the subjects had a resting period of 5 minutes, breathing normal room air.
Thereafter, they were connected to the spirometer, filled with 6 liters of an initial gas mixture of 93% O2 and 7% CO2. Their noses were occluded with a nose clip and they were asked to rebreathe from the spirometer as they wished for a period of 3 minutes.

Measurements

The pulmonary tests were recorded and analyzed using a preprogrammed computer system for pulmonary analysis (Gould Pulmonary Analysis Computer, including a Sharp PC 1500A pocket computer).
During the rebreathing test ventilation was measured with the spirometer, while the end-tidal pCO2 was continuously monitored using a Gould Godart Capnograph MARK III.
The respiratory response to CO2 was assessed according to Read's method (Read, 1967). After an equilibration period of 40 seconds from the start of rebreathing, minute ventilation (VE) was calculated by multiplying average tidal volume and respiratory frequency at 20-second intervals along the rebreathing run. For each measurement point VE was plotted against the corresponding partial pressure of the end-tidal CO2 (PET CO2).
The slope of the regression line (RCO2) for the 7 to 9 points obtained was calculated by means of the least-squares method. Only those regression lines with a product correlation coefficient (R) corresponding to a level of significance of at least 0.05 were included.

Separate regression analyses were performed for changes in tidal volume and respiratory frequency as a consequence of increasing CO2 concentrations. The slopes of the resulting regression lines were taken as measures for the sensitivity for tidal volume (R_TCO2) and respiratory frequency (R_fCO2) respectively.
For additional information the PD subjects were asked to fill in a self rating scale for depression (SDS; Zung, 1965) before the experiment.
Relationships between variables were assessed by calculating Pearson correlation coefficients.

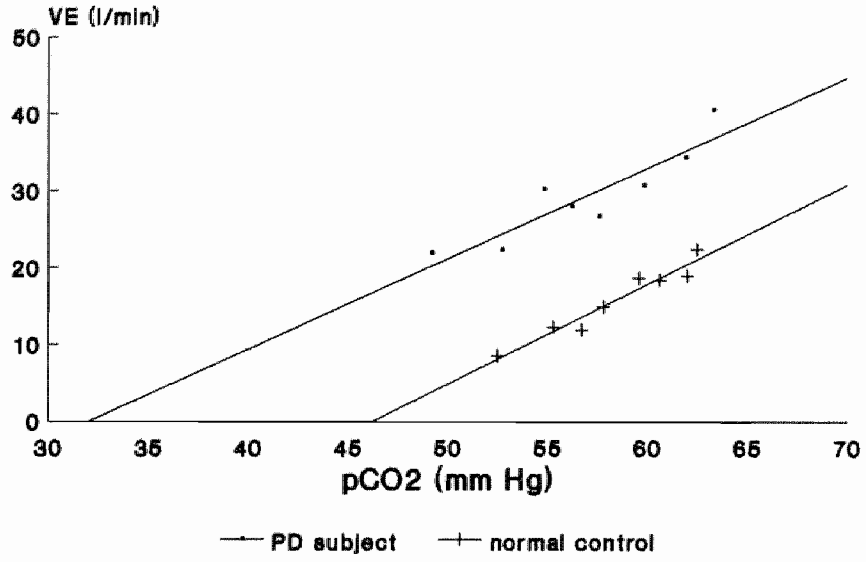

Figure 1. Two examples of regression lines.
- PD subject: male, 26 years, RCO2=1.18, pCO2 intercept = 32.08 mmHg
- normal control: female, 37 years, RCO2=1.29, pCO2 intercept = 46.18 mmHg

Table 1. Comparison between the experimental groups (values of parameters are expressed as means ± standard deviation).

	PD group n=15 8 men 7 women	OCD group n=15 3 men 12 women	normals n=15 8 men 7 women	one-way ANOVA	t-test PD vs. normals
age (years)	31.0 ± 4.91	31.2 ± 10.1	30.7 ± 6.92	p=0.986	p=0.904
height (m)	1.75 ± 0.08	1.69 ± 0.08	1.77 ± 0.10	p=0.056	p=0.496
weight (kg)	71.8 ± 13.3	60.6 ± 8.3	68.5 ± 9.4	p=0.017*	p=0.433
body surface (m2)	1.86 ± 0.17	1.70 ± 0.14	1.84 ± 0.16	p=0.011*	p=0.753
FVC (liters)	4.00 ± 0.94	3.81 ± 0.60	4.68 ± 1.07	p=0.027*	p=0.077
FEV1 (liters)	3.24 ± 0.84	3.06 ± 0.98	3.82 ± 0.82	p=0.061	p=0.068
RCO2 (l/min.mm Hg)	2.27 ± 1.14	2.18 ± 0.96	2.72 ± 1.44	p=0.399	p=0.350
RCO2/FVC (l/min.mm Hg)	0.58 ± 0.29	0.56 ± 0.22	0.60 ± 0.32	p=0.923	p=0.876
RCO2/body surf. ($l/min.mmHg.m^2$)	1.19 ± 0.56	1.27 ± 0.59	1.46 ± 0.73	p=0.484	p=0.260
RCO2/ FVC.body surf. ($l/min.mmHg.m^2$)	0.31 ± 0.15	0.33 ± 0.14	0.33 ± 0.17	p=0.899	p=0.736
R_TCO2 (l/mm Hg)	0.073 ± 0.056	0.084 ± 0.052	0.095 ± 0.051	p=0.542	p=0.281
R_fCO2 (l/min.mm Hg)	0.58 ± 0.41	0.72 ± 0.79	0.87 ± 0.74	p=0.488	p=0.188
extrapolated pCO2 intercept (VE=0)(mm Hg)	41.4 ± 5.9	44.5 ± 4.6	46.4 ± 5.3	p=0.044*	p=0.022*

* significant differences ANOVA or t-test, two-tailed.
R_TCO2 = sensitivity due to the tidal volume component
R_fCO2 = sensitivity due to the respiratory frequency component

RESULTS

Two PD patients, one man and one woman, were excluded because of poor regression lines; they had RCO2 values of 0.77 and 0.43. One OCD patient refused to participate as she was afraid that the mouth piece might contaminate her. These dropouts were replaced by others.

Two PD patients stopped before the 3 minutes ended: one man had trouble breathing at the end of rebreathing due to an orthopedic corset, leaving 7 usable measurement points; one woman could not bear the procedure any longer after 6 measurement points were obtained. None of the subjects panicked during rebreathing.

For the subjects who were included in the analysis, the correlation coefficients between pCO2 and minute volume (means and standard deviations) were similar in each group: 0.946 ($\pm$ 0.041) for PD patients, 0.924 ($\pm$ 0.058) for OCD patients, and 0.951 ($\pm$ 0.047) for normal controls.

Using one-way ANOVA, no significant differences were found with respect to age, height, or FEV1 between the PD, OCD, and the normal group (table 1). Using t-tests, there were no significant differences between the PD group and the group of healthy controls for weight, body surface, or FVC (table 1).

Fig. 1 gives illustrations of regression points and lines of 2 subjects: one male PD patient of 26 years with a low pCO2 intercept (32.08 mm Hg), and one female healthy normal of 37 years with a high pCO2 intercept (46.18 mm Hg).

The RCO2 data are shown in table 1. Analysis by means of one-way ANOVA revealed no significant difference for RCO2 ($F=0.940$, $df=2,42$, $p=0.399$). No differences were found either when RCO2 was expressed as a ratio of subjects' FVC (RCO2/FVC, $F=0.080$, $df=2,42$, $p=0.923$), body surface (RCO2/body surface, $F=0.739$, $df=2,42$, $p=0.484$), or as a ratio of subjects FVC ánd body surface (RCO2/FVC.body surface, $F=0.106$, $df=2,42$, $p=0.899$).

Re-analysis of RCO2 and RCO2/FVC for men and women separately showed no significant differences between PD, OCD, or the normal group either.

Sensitivities due to the tidal volume component (R_TCO2) and the respiratory frequency component (R_fCO2) were similar in each group ($F=0.621$, $df=2,42$, $p=0.542$ for R_TCO2; $F=0.729$, $df=2,42$, $p=0.488$ for R_fCO2).

The extrapolated pCO2 intercept, indicating the hypothetical pCO2 providing zero stimulus to ventilation, was significantly different between the three groups ($F=3.364$, $df=2,42$, $p=0.044$), there being a significant difference between the PD group and the normal control group ($t=2.42$, $df=28$, $p=0.022$).

In the PD group the Pearson correlation coefficients between RCO2, R_TCO2 and R_fRCO2 on the one hand, and the score on the SDS on the other hand were -0.333 ($p=0.112$), -0.1594 ($p=0.285$), and -0.0013 ($p=0.498$) respectively.

DISCUSSION

In the present study PD patients, OCD patients, and normal controls did not differ significantly in RCO2. Re-analysis after correction for FVC and/or body surface, or analysing men and women separately revealed no significant differences either.

Therefore, our earlier findings, which showed a significantly higher RCO2 in PD

subjects than in normal controls (Lousberg et al., 1988), could not be replicated. Comparing the values of RCO2 in these two reports, it is clear that the PD patients in the earlier study had a higher RCO2 than the PD subjects in the present one, while the RCO2 in the previous normal group seems to correspond with the values found in the present healthy control and PD subjects. If the two dropouts due to poor regression lines had been included in the present PD sample, the RCO2 in the PD group would even have been lower. There seem to be no obvious reasons why our earlier results could not be replicated. Patients were referred and diagnosed in a similar way, the techniques used in both studies were identical, and the numbers of subjects were comparable. The present results seem to be more consistent with those found by Woods et al. (1986) and Pain et al. (1988). However, we could not replicate Pain's findings of differences in the tidal volume and respiratory frequency components of RCO2 between PD subjects and normals.

In contrast with the reports of Lousberg et al. (1988) and of Woods et al. (1986), the value of the hypothetical pCO2 corresponding with zero ventilation was significantly lower in PD patients than in normal controls. This could indicate that chemoreceptors of PD subjects have a lower set point than normals. However, the value of 46.4 mm Hg in normals seems rather high, as a pCO2 of 40 mm Hg is a normal level where a CO2 stimulus to breathing would certainly be expected. In addition, Lousberg et al. (1988) and Woods et al. (1986) found values of 39.5 and 37.4 mm Hg, respectively, for the extrapolated pCO2 intercept in normal controls. Therefore, the difference in pCO2 intercepts in the present study should be regarded with some caution.

Many factors have been proven to influence ventilatory response to CO2, such as, for instance, sex (Irsigler, 1976; Damas-Mora et al., 1978), age (Damas-Mora et al., 1978), body surface (Damas-Mora et al, 1978), vital capacity (Irsigler, 1976), personality factors (Saunders et al., 1972; Shersow et al., 1973; Singh, 1984), possible concommitant depression (reducing RCO2) (Shersow et al., 1976; Damas-Mora et al., 1978), drugs (Lambertsen, 1964) and hormones (Lambertsen, 1964).

The PD group and the normal group in the present study were quite similar with respect to most of these parameters (fig. 1), but, unfortunately, it was impossible to control for all variables. Although there was no significant correlation between RCO2 and the SDS value in the PD group and none of the PD subjects were suffering from a major depressive episode, many PD patients did have a borderline score on the SDS. Therefore, it is possible that a tendency towards increased RCO2, due to PD, is blunted by concommitant depressive symptomatology. Possibly, personality factors might also have masked potential differences. The influence of so many factors on RCO2, together with the absence of significant differences in RCO2 in the present study, might suggest that RCO2 may not be the most adequate parameter of chemoreceptor sensitivity.

It could also be argued that Read's rebreathing technique is not the most appropriate method for assessing RCO2, and consequently for determining a potential difference in chemosensitivity. Since significant differences were found by means of the steady-state canopy procedure in small subject samples (Papp et al., 1989), this latter method might be more reliable. Unfortunately, the steady-state method seems to be less standardized than the rebreathing technique (Read, 1967). In the canopy procedure, as described by Gorman et al. (1988) and Papp et al. (1989), the experimental subject's head was placed in a clear plastic canopy that was vented with fresh air and a gas mixture of 5% CO2 respectively. The canopy was connected to a spirometer, permitting measurement of

minute volume. Values of pCO2 were assessed using blood obtained by arterial lines. According to Gorman et al. (1988) and Papp et al. (1989) an important advantage of this method is that the canopy does not induce anxiety (Kinney, 1980), whereas the mouthpiece-noseclip arrangement can be anxiogenic (Askanazi et al., 1980). In addition, they argue that arterial blood gives the most accurate measurement of pCO2. However, the steady-state canopy procedure has various disadvantages: placing arterial lines is painful, it is difficult to perform, and it carries a small risk of thrombus formation. In addition, it may induce anxiety, which would counteract the possible advantage of using a canopy.

Finally, the possible heterogeneity of the PD syndrome (Lelliot & Bass, 1990) and the large variability of RCO2 values may also have contributed to the absence of significant differences in the present study.

In conclusion, to date, data on chemosensitivity to CO2 in PD are inconclusive. Additional research on hypersensitive central chemoreceptors, and their possible relationship to PD is warranted.

ACKNOWLEDGEMENTS

We are grateful to Dr. D. Klein for his comments on an earlier version of this report.

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2.3.3 Increased lifetime prevalence of respiratory diseases in panic disorder?

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American Journal of Psychiatry, Clinical and Research Report, in press

ABSTRACT

Current and past frequency of respiratory diseases were assessed in 30 panic disorder (PD), 30 obsessive-compulsive disorder (OCD) and 30 eating disorder (ED) patients. Lifetime prevalence of respiratory disorders was significantly higher in PD (47 %) than in either OCD (13 %) or ED (13 %). Point prevalences showed no differences.

INTRODUCTION

There is considerable resemblance between the symptomatology of panic disorder (PD) and some diseases affecting the respiratory system. Dyspnea, choking, and smothering sensations are among the most important features common to both. Anxiety, a predominant symptom of PD, also occurs in asthmatic patients (1), in whom it is considered to be of a secondary nature. Strong evidence exists that disturbances in respiratory control, such as hyperventilation, are common to both PD (2) and asthmatic disorders (3).

This resemblance in symptomatology could point to some overlap in pathophysiology, or at least to a relationship between PD and some respiratory disorders. Additional evidence for this comes from recent research on co-morbidity of diseases affecting the respiratory system and PD. Karajgi et al. found that the prevalence of PD was higher in a group of patients with chronic obstructive pulmonary disease (COPD) than in the general population (4).

The present study explored the inverse, i.e. the prevalence of respiratory diseases in PD patients. Past and present frequencies of disturbances in the respiratory tract were assessed in PD, and compared with those found in obsessive compulsive disorder (OCD) and eating disorder (ED).

Our hypothesis was that both lifetime and point prevalence of respiratory diseases would be higher in PD than in either OCD or ED.

METHODS

Data were obtained by means of a retrospective file study. Subjects were chosen from the outpatient files at the Academic Anxiety Center of the Vijverdal Psychiatric Hospital; the 30 most recently referred patients for each group were selected. The first group consisted of 30 PD patients with or without agoraphobia (11 men and 19 women, aged 35.5 $\pm$ 10.1 years). Two comparison groups were included, one consisting of 30 OCD patients (11 men and 19 women, aged 34.3 $\pm$ 10.01 years) and another of 30 ED patients (2 men and 28 women, aged 25.5 $\pm$ 5.4 years). All subjects had been diagnosed by experienced clinicians using the criteria of the DSM-III-R. A full medical history was taken, and a complete physical examination done on each patient.

Point and lifetime prevalence of respiratory disorders (asthma, bronchitis, allergy, pneumonia) were assessed in each group. Since the ED group was significantly younger than the other groups, childhood prevalence (before the age of 16) was also calculated.

The results were analyzed using the chi-square test.

RESULTS

Table 1 shows the point, lifetime, and childhood prevalences of respiratory diseases in each group.

Lifetime prevalences were significantly different between the three groups (chi-square = 12.03, df=2, $p<0.005$); this was obviously due to the higher value in the PD group.

It is likely that these findings were related to a higher childhood prevalence (chi-square = 9.74, df=2, $p<0.01$).

No differences were found between the three groups with respect to point prevalences (chi-square = 0.856, df=2, non-significant).

Table 1. Prevalences of respiratory disorders.

	PD(n=30)	OCD(n=30)	ED (n=30)	level of significance (chi-square)
point prevalence	3 (10%)	2 (7%)	2 (7%)	N.S.
lifetime prevalence*	14 (47%)	4 (13%)	4 (13%)	$p < 0.005$
childhood prevalence	12 (40%)	4 (13%)	3 (10%)	$p < 0.01$

PD = panic disorder; OCD = obsessive-compulsive disorder;
ED = eating disorder
* 7 PD, 3 OCD and 1 ED patient had a history of asthma

DISCUSSION

In the present study PD, OCD and ED patients showed no differences in point prevalence of respiratory disorders. The frequency found of 7%-10% seems to correspond to that found in the general adult population (40-70 years) for chronic bronchitis (17% in men and 7% in women) and wheeze occuring at least once a week (9% in men and 3% in women)(5). Comparison with the Littlejohns' study should be viewed with some caution as different methods and older subjects were used. Nevertheless, it seems reasonable to conclude that point prevalences are not markedly increased in PD, OCD, or ED.

In contrast with point prevalence, lifetime prevalence was impressively higher in PD than in either OCD or ED. Childhood prevalences were compared due to the approximately 10 year age difference existing between the ED and the other two; similar results were obtained.

These results are quite noteworthy. The development of PD would seem to be associated with a history of respiratory illness in childhood, disorders which share many of the symptoms found in PD.

It could be speculated that the disturbed respiratory physiology in COPD plays a role in the pathogenesis of PD. Severe cases of asthma can induce hypercapnia (3), while in adult PD patients exogenous CO2 administration provokes an important increase in

anxiety (6). There is strong evidence in favor of a genetic predisposition to developing PD (7). This predisposition might consist of a hypersensitivity of some CNS structures, such as the locus ceruleus, to CO2 loading, inducing heightened anxiety. Taken together, it could be hypothesized that repetitive or chronic hypercapnia during obstructive pulmonary diseases in childhood may induce physiological changes in respiratory control, or bad breathing habits. The resulting CO2 fluctuations would then facilitate the development of PD in subjects who are already genetically vulnerable to this disease.

Alternatively, it could be speculated that disorders affecting the respiratory system predispose one to develop PD merely by means of a learning effect. People who suffered from respiratory diseases in childhood often had accompanying fearful physical experiences during acute episodes of their illness. Later, when a slight arousal occurs accompanied by symptoms resembling those of their earlier frightening periods, they may become anxious. It is possible that this conditioning effect is not limited to respiratory diseases alone but perhaps also concerns other physical problems, such as minor vestibular or cardiac problems. This hypothesis is supported by the finding that the frequency of vestibular disorders appears to be increased in PD (8; Griez et al., unpublished report), while mitralis prolapse is also often diagnosed in PD patients (9). Although the latter studies do not establish the exact causal relationship, it could be speculated that development of PD can be facilitated by various somatic disorders, possibly by means of conditioning mechanisms.

The present study has its limitations: the number of subjects is small and data were obtained by means of a retrospective file study. Furthermore, it could be argued that PD subjects reported higher frequency of respiratory diseases due to hypochondriacal tendencies in PD patients; yet the same should then hold true for other symptomatology. Additional research to history of diseases in general in PD and, for instance, other anxiety disorders seems therefore necessary. Furthermore, it would be of interest to investigate whether the panic symptom profile of PD patients with a history of respiratory diseases show a predominance of respiratory type symptoms. These matters are presently being addressed in additional studies in our laboratories. Until these questions have been resolved the conclusions of the present study are of a preliminary nature.

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CHAPTER 3:

THEORETICAL CONSIDERATIONS

Effect of hypercapnia and other disturbances in the acid-base balance on panic disorder

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Hillside Journal of Clinical Psychiatry, 11:185-197, 1989

Hillside Journal of Clinical Psychiatry, 11(2), Fall/Winter 1989

Effect of Hypercapnia and Other Disturbances in the Acid-Base-Balance on Panic Disorder

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ABSTRACT: Naturally occurring panic attacks and various interventions which trigger anxiety in panic patients are accompanied by disturbances in the acid-base balance. Carbon dioxide appears to play an important role in many experimental panic provoking conditions. The influence of respiratory and metabolic pH disturbances on cerebral physiology is discussed and speculations are made about the possible mechanisms underlying CO_2-induced anxiety in panic disorder.

KEY WORDS: Panic disorder; Acid-base balance; pH; Carbon dioxide; Hyperventilation; Lactate.

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Introduction

With the publication of the DSM-III in 1980, panic disorder (PD) became officially recognized as a separate diagnostic entity (APA, 1980). According to the revised version of the DSM-IIIR (APA, 1987), PD exists with or without avoidance (agoraphobia). The symptoms usually appear in the following sequence: (1) panic attacks, (2) panic attacks + anticipatory anxiety (phobophobia), and (3) panic attacks + anticipatory anxiety + avoidance (agoraphobia). In phases 2 and 3 panic attacks are often no longer the most predominant symptom.

In spite of the great deal of research that has been carried out in PD, the cause of this syndrome is still unknown; however, it seems that both psychological and biological factors are involved. Among the psychological explanations for PD one finds the concepts of the interoceptive phobia in panic patients or, in other words "fear of symptoms" or "fear of fear" (Ley, 1987; van den Hout et al., 1987) and "catastrophic misinterpretation" (Clark, 1986). Once a panic attack is triggered, the somatic arousal symptoms cause anxiety which, in turn, causes more symptoms. However, the triggering, or onset, of a panic attack is much more difficult to explain psychologically (Griez & Vroemen, 1986).

Other theories refer to a biological vulnerability to various substances in PD. Interventions which can be used to induce anxiety in susceptible patients include yohimbine, caffeine, isoprotenerol, CO_2 inhalation, lactate infusion, and possibly hyperventilation provocation (Woods et al., 1986; Shear, 1986).

The first three substances appear to influence the brain directly in a pharmacological way. In this article, the relationships between the last three provocation mechanisms and panic will be discussed in more detail from a neurophysiological perspective.

Hyperventilation

Panic disorder appears to be closely related to the hyperventilation syndrome. It has, in fact, been shown that naturally occurring panic attacks can be accompanied by hyperventilation (Salkovsis et al., 1986; Griez et al., 1987a; Hibbert & Pilsbury 1988).

Many people regard hyperventilation itself as the cause of the anxiety and other symptoms in the hyperventilation syndrome and/or PD

(Beumer & Hardonk, 1980; Hibbert, 1984; Folgering, 1986). According to Ley, the symptoms of hyperventilatory hypocapnia precede the experience of fear, and he postulates that a panic attack consists of a synergistic interaction between hyperventilation and fear (Ley, 1985). He also suggest that a change in pH in the range of 7.4 to 7.6, and/or a change in pCO_2 in the range of 40-20 mm Hg, causes little increase in symptoms. However, when the pH exceeds 7.6 and /or the pCO_2 drops below 20 mm Hg, an increase in pH and/or a decrease in pCO_2 results in a dramatic change in symptoms (Ley, 1986).

On the other hand, several reports have suggested that hyperventilation is not very panicogenic (Gorman et al., 1984a, 1988; Griez et al., 1988; Zandbergen et al., 1990). Gorman et al. (1984a, 1988) found that during hyperventilation provocation, panic developed in only a few patients, while both lactate infusions and 5% CO_2 were much more panicogenic. Griez et al (1988) noticed that voluntary hyperventilation caused some increase in anxiety in panic patients. However, these changes were small. In normals there was also a small rise in anxiety.

Zandbergen et al. (1990) subjected PD patients and normals to a hyperventilation provocation test as well as to a 35% CO_2 challenge. Anxiety following one CO_2 inhalation in panic patients was significantly higher than the response in the other three conditions (i.e. hyperventilation in PD patients, CO_2 in normals, and hyperventilation in normals). There was no significant difference in the latter three conditions.

In summary, although panic can be accompanied by hyperventilation, it seems that hyperventilation does not induce panic in PD subjects.

Lactate

At present, lactate provocation is one of the best known and most extensively studied models for panic anxiety. The study by Pitts and McClure (1967) has been replicated and discussed many times (Fink et al., 1970; Kelly et al., 1971; Arbab et al., 1971; Bonn & Harrison, 1971; Knott et al., 1981; Gorman et al., 1984a; Liebowitz et al., 1984). Lactate has proved to be very successful in provoking panic, even though one report does not support this (Ehlers et al., 1985).

The original underlying idea was that lactic acid might play a role in the pathogenesis of naturally occurring panic attacks (Pitts & Mc-

Clure, 1967). Indeed, Holmgren and Strom (1959) had observed that although there is no difference in blood lactic acid between patients and normals in a state of rest, exercise causes a greater increase in lactic acid in patients than it does in normals. Apparently, one did not take into account the fact that exogenous administration of lactate is not equivalent to lactacidaemia, one of the differences being the opposite effects thay have on the blood pH.

Pitts and McClure (1967) found another explanation. They assumed that the decrease in plasma Ca^{++} caused the symptoms during lactate infusion. This was supported by their finding that adding Ca^{++} to the lactate infusion resulted in fewer symptoms. However, Grosz and Farmer (1969) argued that the decrease in Ca^{++} concentration was too small to explain the symptoms. Furthermore, EDTA, a powerful calcium chelator, has not succeeded in triggering anxiety. On the other hand, it seems that verapamil, a calcium channel blocker, may have modest antianxiety and antipanic properties (Klein & Uhde, 1988).

In another experiment, Grosz and Farmer (1972) found that, in normals, symptoms like paresthesias, tremors, shakiness, dizziness, and palpitations were provoked not only by lactate infusion but also by an HCO_3 infusion. They argued that the alkalosis could explain the symptoms. This hypothesis may be supported by a recent study, in which bicarbonate infusions induced panic in 9 of 20 PD patients (Gorman et al., 1989). Yet, some contradictory findings were found here as well. Firstly, Liebowitz et al. (1986) noticed that patients who panicked during lactate infusion did not develop a greater alkalosis at the onset of panic than non-panicking PD patients. Secondly, as mentioned above, hyperventilation provocation, inducing considerable alkalosis, fails to provoke panic. Thirdly, among the effects of alkalosis is a decrease in cerebral blood flow (Guyton, 1976; Hauge et al, 1980), as well as in coronary blood flow (Yashue et al., 1978; Mudge et al., 1979). However, it has been demonstrated that lactate, rather than reducing the cerebral blood flow, actually increases it in normals and non-panicking PD patients; even patients who experience panic showed a small increase (Stewart et al., 1988). Finally, it seems logical to suggest that, because of the metabolic alkalosis, there is some sort of respiratory compensation, namely hyperventilation. However, during lactate infusion people start to hyperventilate, which causes even greater alkalosis. This phenomenon happens in both patients and normals, although patients hyperventilate more (Gorman et al., 1986).

Several other theories have been postulated to explain why lactate infusion is a panicogenic intervention. One of these theories suggests that lactate has a direct influence on the cerebrum. Though lactate passes the blood-brain barrier slowly and in small amounts, there is definitely some transport by means of stereospecific active mechanisms (Partridge, 1983; Lingjaerde, 1985). Lingjaerde (1985) has suggested that lactate might stimulate serotonin re-uptake, resulting in a reduction in serotonin activity.

Other theories about the panicogenic capacity of lactate, which have been postulated as a reaction to experiments with carbon dioxide in panic, will be discussed in the next section.

CO_2

In recent years it has become clear that CO_2 is also an efficient means of provoking anxiety in PD patients.

Gorman et al. (1984a) had their subjects breathe 5% CO_2. As a result, their respiration rate increased 300%, while their pH remained about the same. In 7 out of 12 patients this caused panic, while 8 of 12 panicked with lactate and 3 out of 12 panicked during room air hyperventilation. An extension of this experiment (Gorman et al., 1988) showed similar results.

An experiment by Woods et al. (1988) also demonstrated the panicogenic capacity of 5% CO_2 in panic patients. Moreover, it demonstrates 7.5% CO_2 might induce considerable anxiety in normals as well. The authors suggest that the mechanisms underlying CO_2-induced anxiety may be similar both in patients with PD and in healthy subjects; however, some of the patients may have a lower threshold for the activation of the CO_2 anxiogenic mechanisms.

Griez et al. (1987b, 1990a, 1990b) demonstrated that in panic patients one vital capacity 35% CO_2/65% O_2 inhalation provoked anxiety and symptoms that were quite similar to real-life panic attacks. No anxiety was induced in normals, obsessive compulsive disorder (OCD) patients and a mixed anxiety group including OCD patients and social phobics. The pH decreased to about 7.1 and there was a rise in both Ca^{++} and K^{+} (Griez et al., 1987c). This experiment has been replicated by others (Fyer et al., 1987).

Because CO_2 passes the blood-brain barrier rather easily, a rise in pCO_2 will result in both a peripheral and central acidosis. The observation of significant reductions in skin, salivary, and urinary pH dur-

ing stressful situations (Sandin & Chorot, 1985) is another indication that a central acidosis may be involved in panic anxiety.

There are even good arguments supporting the idea that lactate infusions result in a central acidosis. Carr and Sheehan (1984) argue that lactate infusions influence the reaction:

$$\text{pyruvate} + \text{NADH} + \text{H}^{+} \longleftrightarrow \text{lactate} + \text{NAD}+$$

This could result in a decrease in pH in such essential regions as the chemoregulatory zones. Furthermore they suggest that PD patients could be hypersensitive to CO_2 and lactate, perhaps due to a defect in the intracellular redox regulation system.

Gorman et al. (1984b) also argue that lactate might be metabolized into pyruvate, but mainly in organs like the liver. This pyruvate would then be transformed into HCO_3-, which is in a dynamic equilibrium with CO_2. Because CO_2 diffuses to the brain very easily, this would result in an increase in central pCO_2 and in a central acidosis.

The assumption that central acidosis is one of the underlying mechanisms in panic is supported by the finding that a decrease in pH stimulates serotonin re-uptake, resulting in a reduction in serotonin activity (Lingjaerde, 1985).

On the basis of all this information, Carr and Sheehan (1984) speculated that the course of events in a panic attack might be as follows: medullary chemoreceptor pH drop and/or inappropriate triggering of respiratory cascade → arousal/anxiety → further ventilation → hypocarbia → alkalosis → central ischemia and a rise in the lactate/pyruvate ratio → a further drop in central pH. . . .

Consequently, this model would also explain the role of hyperventilation in panic attacks.

In summary, CO_2, like lactate, is very powerful in provoking anxiety in panic patients. Central acidosis may well play an important role in panic.

Effect of CO_2 and H+ on the Normal Cerebrum

Since CO_2 has proved to be so effective in the experimental provocation of panic, it seems logical to examine the physiology of the chemoreceptive areas within the CNS and the influence of CO_2 on other parts of the cerebrum.

Influence of Blood pCO_2/pH on Brain Fluids and the Central Chemoreceptors.

It has been shown that respiratory alkalosis/acidosis has a rapid effect (within minutes) on cerebrospinal fluid (CSF) pH, while metabolic alkalosis/acidosis has a much smaller and slower effect (after several hours; Guyton, 1976; Nattie, 1983)

The effect of acid-base disturbances may be greater in a few specific parts of the brain, such as the chemoreceptor zone at the ventral medullary side, where the structure of the blood-vessels allows more diffusion. In this area, respiratory acid-base disturbances have a very rapid influence on the ISF pH (within a few seconds), on the activity of the phrenic nerve, and on ventilatory responses (Teppema et al., 1983; Kiley et al., 1985).

Metabolic acid-base disturbances also have a fairly rapid influence on the ISF pH in this chemoreceptor zone (within a few minutes), although the change seems to be less than the corresponding [H+] (and/or [HCO_3-]) change in the blood (Ahmad et al., 1976; Javaheri et al., 1981; Teppema et al., 1983; Eldridge et al., 1985). An increase in pCO_2 and a decrease in pH both cause an increase in respiratory activity (Guyton, 1976; Schläfke, 1976).

Until recently it was believed that the H+ concentration in the ISF was the unique stimulus for respiration and that the difference in effect between respiratory and metabolic acid-base disturbances stemmed only from the fact that CO_2 diffuses faster through the blood-brain barrier than H+ (Guyton, 1976; Schmidt & Thews, 1980; Loeschke, 1982). However, recent studies indicate the possible existence of different chemoreceptive structures for CO_2 and H+ (Teppema et al., 1983; Harada et al., 1985; Eldridge et al., 1985).

Influence of CO_2 and H+ on Nerve Activity

In addition to their influence by means of central chemoreceptors, carbon dioxide and H+ have a direct effect on neural activity, such as the polarization/excitability of neurons. Carbon dioxide easily diffuses to all parts of the brain (Guyton, 1976; Nattie, 1983). It seems that a sudden increase in pCO_2—and perhaps a sudden decrease as well—results in a hyperexcitability of all neuronal cells (Woodbury & Karler, 1960; Krnjevic et al., 1965) which, in general, leads to a slight depolarization. Moreover, it increases (nor)adrenergic activity in particular (Tenney, 1960; Elam et al., 1981).

Relationship between pH/pCO_2 and Cerebral Blood Flow

An important factor in the regulation of the acid-base status of the brain is cerebral blood flow. A decrease in blood pH or an increase in blood pCO_2 will result in a higher cerebral blood flow, while an increase in blood pH or a decrease in blood pCO_2 results in a lower cerebral blood flow (Guyton, 1976; Hauge et al., 1980). It appears that lactate also increases the blood flow (Stewart et at., 1988), something which is inconsistent with a metabolic alkalosis but more indicative of a central acidosis. Biochemically, vasodilatation should not have many consequences, except perhaps a decrease in pCO_2. Vasconstriction tends to result in an increase in pCO_2, decrease in pH and a decrease in pO_2.

It is interesting that in normals both hyperventilation provocation and CO_2 inhalation cause a feeling of lightheadedness and some dizziness, symptoms which may be related to cerebral blood flow.

The innervation of cerebral blood vessels appears to include noradrenergic and serotonergic nerves. Noradrenaline seems to have a regulatory effect on cerebral blood flow; the exact role of serotonin, however, is not quite clear (Marco et al., 1985). In other tissues, serotonin can have both vasodilatory and vasoconstrictive effects (Guyton, 1976; Giertz et al., 1980).

Discussion

It has been well established that CO_2 is very efficient in provoking panic in PD patients. The precise mechanisms of this hypersensitivity to CO_2 however remain unclear. Therefore, this discussion will be limited to merely reviewing the various theories that have been advanced over the past years.

Thus far, most explanations have favored the hypothesis that CO_2 must have a special influence on a specific anatomical and/or pharmacological structure that is specifically involved in panic disorder. One of the first such hypotheses was that the locus ceruleus might be involved in PD (Gorman et al., 1984b). Moreover, it has been demonstrated that CO_2 increases the activity of either the locus ceruleus (Elam et al., 1981) or its metabolites (Sechzer et al., 1960). Taken together, these findings may explain the panic provoking property of CO_2 in PD (Gorman et al., 1984a).

As mentioned above, another theory suggests that the activity of

the serotonergic system might be reduced in PD (Lingjaerde, 1985; Pols & Griez, 1988). This theory is in line with the finding that CO_2 probably results in a rise in the serotonin re-uptake, which means a decrease in the activity of serotonin (Lingjaerde 1985).

A third hypothesis to explain panic is the postulation of chemoreceptors hypersensitive to CO_2 in PD (Carr & Sheehan 1984, Woods et al., 1986, Gorman et al., 1988). This theory is supported by a study in which an increased sensitivity to CO_2 in panic, as measured by ventilatory responses, was observed (Lousberg et al., 1988).

On the basis of these three theories, assuming a specific disturbed system in PD, it can be understood that CO_2 is a panicogenic substance in panic disorder.

However, it has never clearly been demonstrated that there is one basic specific underlying lesion in PD. Nevertheless, the panicogenic capacity of CO_2 might be understood whether or not CO_2 specifically influences a specific anatomical, pharmacological or physiological structure (Griez et al., 1987b). As mentioned above, carbon dioxide easily diffuses to all parts of the brain (Guyton 1976, Nattie 1983), and it seems that a sudden increase in pCO_2—and perhaps a sudden decrease as well—results in hyperexcitability of neuronal cells (Woodbury & Karler, 1960; Krnjevic et al., 1965) which, in general, means a slight depolarization. Although this happens in all neuronal cells, the effect might be greater is some specific cells which are already slightly depolarized. In PD this could, for instance, be the result of an overactive stimulating system, like the noradrenergic system, or an underactive inhibiting system, like the serotonergic system. In these particular cells, a slight extra depolarization might then lead to one or more action potentials. In other words, these cells would become hypersensitive to CO_2. As a consequence, spontaneous attacks could be triggered by small disturbances in the pCO_2.

In conclusion, in spite of the extensive research that has been conducted over the past years, we do not yet know what exactly happens in panic disorder or why CO_2 is a panic inducing agent in susceptible patients. However, several hypotheses have been postulated and may lead to various lines of research.

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CHAPTER 4: CONCLUSIONS

From the study described in chapter 2.2.1 ("No chronic hyperventilation in panic disorder patients") it can be concluded that, in general, PD patients are not chronic hyperventilators, and that they have no reduced buffering capacity for pH disturbances. In other words, pCO2 changes, as a consequence of a few extra breaths for instance, will not result in greater pH changes in PD subjects than in other anxiety disorder patients, or healthy controls. It also means that the vulnerability of PD patients to inhalation of CO2 can not be attributed to a reduced blood buffering capacity.
The experiments in chapter 2.2.1 ("Effects of low pulmonary CO2 on panic anxiety") and 2.2.2 ("Hypercarbia versus hypocarbia in panic disorder") suggest that, in contrast to experimentally induced hypercarbia, experimental induction of hypocarbia alone is insufficient to induce panic in the majority of PD patients. Together with the results of other studies inside (Gorman et al., 1984a, 1988; Roll, 1987; Hornsveld et al., 1990) as well as outside the laboratory (Hibbert & Pilsbury, 1989; Garssen & Buikhuisen, 1991) it can therefore be concluded that respiratory alkalosis does not play a major role in the pathogenesis of panic. It is more likely that, at least in the majority of PD patients, hyperventilation, should it occur during a panic attack, is a consequence rather than a cause of panic.
The results of the study in chapter 2.2.3 ("An analysis of panic symptoms during hypercarbia compared to hypocarbia in patients with panic attacks") indicate that it is the respiratory symptoms that are of major importance in CO2 induced panic. It could be argued that an inhalation of 35% CO2 has an acute stimulus to respiration and appearance of respiratory symptoms, which in turn lead to anxiety by the principle of "fear of symptoms" (Van den Hout et al., 1987) or "catastrophic misinterpretation" (Clark, 1986). On the other hand, panic symptoms like palpitations, faintness and dizziness, were also clearly provoked by one inhalation of 35% CO2 to an almost comparable degree as respiratory symptoms. According to the cognitive theories of "fear of symptoms" or "catastrophic misinterpretation" these symptoms would be expected to be anxiogenic in PD (Van den Hout et al., 1987). However, it was found that palpitations, faintness and dizziness did not significantly correlate with the anxiety PD subjects experienced. Therefore the results of this study might suggest a specific role of respiratory symptoms in PD, although this speculation should be confirmed by studies in "real-life panic" and by studies which compare anxiety and symptom profiles during CO2 inhalation with challenge tests that have a less direct effect on the occurence of respiratory symptoms. Should the close association between panic and respiratory symptoms be confirmed, it might point to a strong functional relationship between brain structures involved in panic and those in respiratory control.
The main conclusion from the findings in chapter 2.3.1 ("Breath-holding in panic disorder") is that breath-holding can not serve as a simple test supporting the diagnosis of PD in patients with anxiety disorders, as no clear difference was found between PD and other anxiety disorder subjects. It seems that anxiety and/or suffering from an

anxiety disorder is of major influence on breath-holding capacity. However, PD patients did show a trend towards lower breath-holding times with a one-tailed t-test, a finding which could not be attributed to differences in baseline anxiety. Therefore, these results warrant further investigation.
The experiment in chapter 2.3.2 ("Ventilatory response to CO2 in panic disorder") showed neither significant differences in the ventilatory response to CO2, nor in the tidal volume and frequency component of ventilatory response. These findings do not support the hypothesis that PD patients have hypersensitive medullary CO2 receptors. Although PD patients had a significantly lower pCO2 intercept, indicating the hypothetical value with zero stimulus to ventilation, than normals, these findings should be regarded with some caution, as the average value in normals seems unusually high.
The pilot study in 2.3.3 ("Increased lifetime prevalence of respiratory diseases in panic disorder?") suggests that PD patients have suffered more often from respiratory diseases in childhood than OCD and ED patients. Although these results are quite intriguing, they are of a preliminary nature as data were obtained in a relatively small number of subjects by means of a retrospecive file study. Therefore, it can not be excluded that the results were biased by overestimation of respiratory diseases as a consequence of hypochondrical tendencies which often occur in PD patients. These results should therefore be confirmed in a larger number of subjects, preferably in a prospective study. In addition, they should be contrasted with a history of physical diseases, which induce no panic like symptoms. When these questions have been resolved and if the results of the study in 2.3.3 are confirmed, it would be of interest to investigate whether PD patients with a history of respiratory diseases show a panic symptom profile with a predominance of respiratory type symptoms during their naturally occuring panic attacks.

Summarizing the studies described in this thesis, they imply that hyperventilation, neither chronic nor acute, play a major pathogenetic role in panic. In addition, the studies found no clear objective indications of a disturbance in respiratory regulation in PD. Nevertheless, CO2 induced anxiety appeared to correlate best with respiratory symptoms, while preliminary data suggest an association between panic and a history of respiratory diseases.
These findings pose interesting questions for future research, some of which are stated below. Since there are strong arguments in favor of both biological and psychological mechanisms in panic, it would be of interest to investigate the characteristics of the subgroup of PD patients who panic during the 35% CO2 challenge. It could be hypothesized that CO2 inhalation mainly affects those PD patients with a predominance of respiratory symptoms during their natural panic attacks and/or those patients with a history of respiratory diseases. If that would be the case it might point to cognitive mechanisms in panic. Furthermore it might be possible, that, although CO2 sensitivity seems not spectacularly increased in PD in general, the subgroup with increased emotional vulnerability to CO2 inhalation could have altered ventilatory responses to CO2.
In order to further investigate the mechanisms behind CO2 induced panic, it would be interesting to compare the effects of CO2 challenges with other provocation tests, for instance with substances which are supposed to influence specific brain structures. Especially intriguing would then be the question whether these provocation tests affect

the same PD patients as CO2 inhalation, or, alternatively, whether some PD patients panic with CO2, while others may panic with other provocation procedures. The first possibility might be in favor of a central origin of panic with physical symptoms as secondary phenomena, whereas the second alternative might support the importance of cognitive mechanisms in panic.

Although it might lead to practical problems, valuable information could be obtained by an experiment which measures anxiety while inducing dyspnea without influencing the acid-base status of the blood. This would give an indication whether CO2 induced panic is cognitively mediated or whether it directly influences brain structures involved in panic. One method might be inhalation of chemical or mechanical irritants, leading to hyperpnea. Another possibility might be an experiment which requires increased muscular effort for overcoming respiratory resistance.

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DANKWOORD

Aan dit proefschrift hebben vele mensen een bijdrage geleverd. Slechts één daarvan wordt op de voorpagina vermeld. Al die anderen, wiens onontbeerlijke hulp vaak belangeloos werd gegeven, moeten toekijken, hoe die ene persoon met de eer gaat strijken. Gelukkig biedt een proefschrift de mogelijkheid om, door middel van een dankwoord, dit leed enigszins te verzachten.
In de allereerste plaats gaat mijn dank uit naar Eric Griez. Op inspirerende en bezielende wijze werd ik door jou, mijn leermeester, in het wetenschapsbedrijf in al z'n facetten geïntroduceerd en de gehele periode van mijn aanstelling ben je me met raad en daad blijven steunen. Ook op momenten dat onderzoeksproblemen voor mij vrijwel onoverkoombaar leken, hielp je op energieke en kordate wijze om ze op te lossen. Bovendien kreeg ik van jou alle ruimte en middelen om onderzoek te doen. Eric, ik ben je zeer erkentelijk voor dit alles.
Mijn promotoren, Marcel van den Hout en Mark Richartz, ben ik eveneens grote dank verschuldigd. Jullie enthousiaste opmerkingen en adviezen omtrent onderzoek en bovenal het schrijven van het proefschrift, waarbij mij overigens alle ruimte werd gelaten, hebben mij enorm gestimuleerd. Bovendien hebben jullie, als voorzitters van respectievelijk het onderzoeksproject Experimentele Psychopathologie en de vakgroep Klinische Psychiatrie, mede in belangrijke mate bijgedragen aan het creëren van de omstandigheden om onderzoek te doen.
De in dit proefschrift beschreven studies vonden plaats op het Academisch Angstcentrum Vijverdal. Hier werd mij welwillend alle gelegenheid en assistentie geboden om mijn onderzoek uit te voeren. Alle vroegere en huidige medewerkers van het AAC wil ik hiervoor hartelijk danken. Eric, Julien, Louis, François, Ruud, Marianne, Valesca, Nicolette, Ron, Cor, Hanny, Armida, Corien, Manuela, Margo, Taco, Henk, Harold, Cathrien, Isabella en vooral de research-verpleegkundigen Abeth, Jos en Inge, altijd kon ik bij jullie terecht, altijd waren jullie geïnteresseerd in mijn bezigheden, altijd waren jullie bereid mij te helpen. Ik ben jullie zeer erkentelijk voor deze uitermate plezierige samenwerking. Henk Pols, met wie ik zo'n 4 jaar de kamer heb gedeeld, wil ik bovendien bedanken voor de vruchtbare discussies. Henk, jouw formidabele en gedetailleerde kennis op farmacologisch gebied en jouw zuivere methodologische benadering hebben mij voor menige valkuil behoed.
Van de leden van de vakgroep Klinische Psychiatrie die nog niet genoemd zijn, wil ik met name Rob van Diest, Ine Kusters en Jolanda Koch bedanken. Rob, welke vraag ik ook had over computers, methodologie en statistiek, je nam altijd de moeite en tijd om mij dit geduldig uit te leggen. Ine en Jolanda, jullie gemoedelijke, welwillende en vakkundige ondersteuning op secretarieel gebied gedurende de afgelopen jaren hebben mijn werk in hoge mate verlicht. Mijn hartelijke dank hiervoor.
Bij een aantal studies in dit proefschrift heb ik veel hulp gehad van de medisch studenten Michael Bright, Vera van Aalst en Maja Strahm. Jullie, maar ook alle andere studenten die mij de afgelopen jaren behulpzaam zijn geweest: mijn oprechte dank.

Nog vele anderen waren onmisbaar. Pamela Falger-Cohen, Alan Ralston en Isabella Fernandez hebben mijn krakkemikkige Engels op uitstekende wijze gecorrigeerd. Herman Pennings beschikte over een ongelofelijke prikvaardigheid. Angela Verwey en Allert Andela zorgden dat allerlei bureaucratische zaken vlekkeloos verliepen. Jos op 't Root organiseerde op uitstekende wijze vele cursussen. Jullie allen: mijn dank is groot.
Het allerbelangrijkste waren echter de patiënten en proefpersonen die bereid waren in het onderzoek te participeren. Zonder jullie was dit werk absoluut onmogelijk geweest. Hiervoor zal ik jullie altijd dankbaar blijven.

CURRICULUM VITAE

Jan Zandbergen werd op 17 mei 1958 geboren te Drachten. Na het behalen van het atheneum diploma in 1976 studeerde hij twee jaar Natuurkunde aan de Rijksuniversiteit Groningen. In 1980 begon hij de studie Geneeskunde, eveneens aan de Rijksuniversiteit Groningen, waarbij de co-assistentschappen werden gelopen op het ziekenhuis "De Weezenlanden" te Zwolle. In augustus 1987 haalde hij het artsdiploma, waarna hij begon als Assistent-in-Opleiding bij de vakgroep Klinische Psychiatrie van de Rijksuniversiteit te Maastricht. In deze functie werden op het Academisch Angstcentrum Vijverdal de in dit proefschrift beschreven experimenten uitgevoerd.